Medical Lib.

VOLUME 28 • NUMBER 6

ARCHIVES

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DECEMBER 15, 1921

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO, ILLINOIS. ANNUAL SUBSCRIPTION, $5.00

Entered as Second-Class Matter, January 23, 1909, at the Postoffice at Chicago, Illinois, Under Act of Congress of March 3, 1879. Acceptance for mailing at special rate of postage provided for in Section 1103, Act of October 3, 1917, authorized on June 14, 1918.

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Archives of Internal Medicine

VOL. 28 DECEMBER, 1921 No. 6

THE BLOOD IN TETRACHLORETHANE POISONING*

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BOSTON

Tetrachlorethane is a substance that readily poisons man, causing a fatal toxic hepatitis when it enters the body in sufficient amounts. It is used commercially because of its peculiar physical and chemical properties. It is a solvent for cellulose acetate and is both waterproof and noninflammable. Tetrachlorethane has risen to a point of paramount interest in the last few years because of its use in some of the so-called aeroplane "dopes"—the varnish with which the linen wings of aeroplanes are painted.

During the war, numerous cases of poisoning from use of this substance were reported among those engaged in the manufacture of aeroplanes in England, America and Germany. Some deaths occurred from this substance in England and Germany but none have been reported from America. Tetrachlorethane is being utilized in this country in the manufacture of such articles as noninflammable films, various lacquered goods and artificial silk.

The president of an artificial silk plant, employing about sixty persons at one time, requested one of us to supervise for five months an investigation of the health of his employees, aiming particularly to learn how to prevent any serious form of tetrachlorethane poisoning. The general clinical aspects of this investigation have been conducted by Dr. Derric C. Parmenter.[1] The part of this general investigation that is reported here was undertaken by us to determine whether tetrachlorethane produced any abnormality of the blood; and, if so, whether mild poisoning could be detected or even anticipated by blood examination. It was hoped that a blood examination might be of value in aiding the regulation of employment in such a plant.

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* From the Medical Laboratories of the Massachusetts General Hospital.

* This is paper No. 2 of a series of studies on the physiology and pathology of the blood from the Harvard Medical School and allied hospitals, a part of the expense of which has been defrayed from a grant from the Proctor Fund of the Harvard Medical School, for the Study of Chronic Disease.

* Presented in abstract before the Association of American Physicians, Atlantic City, N. J., May 11, 1921.

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Because tetrachlorethane may produce a toxic hepatitis somewhat similar to that which may be produced by arsenobenzol, arsphenamin, etc., it was thought that the blood of tetrachlorethane workers might show increases of large mononuclear cells, as Evans [2] and one of us has observed occasionally occurs with the initial stages of poisoning from these arsenic products. It was also thought that blood changes in the nature of destruction of red cells, with increased marrow activity, might occur like those due to trinitrotoluene,[3] dinitrophenol and dinitrobenzene, substances which produce a toxic hepatitis.

Before discussing the blood findings in the sixty-eight persons we have studied, who were exposed and some who were poisoned by tetrachlorethane, it is desirable to summarize briefly the symptomatology and pathology of tetrachlorethane poisoning.

From the literature, which is chiefly made up of reports by Wilcox [4] and others,[5] a summary by Hamilton,[6] and by reports from Jungfer,[7] Grimm, Heffter and Joachimoglu,[8] and Koelsch,[9] we obtained a fairly good clinical picture of particularly the severer tetrachlorethane poisoning.

The subjects of our study have given us a clearer picture of the early symptomatology of this form of industrial poison than can be obtained from the literature.

The earlier symptoms consist of three chief types, general, gastric and nervous. In a typical case, the onset is marked by a sense of

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abnormal fatigue; the patient perspires freely; drowsiness develops, with loss of appetite, nausea, vomiting, constipation and headache. After days, or even weeks, jaundice develops, and the gastric and nervous symptoms increase. There then may be confusion, delirium, coma and death. The preliminary symptoms of abnormal fatigue, general discontent and nervousness, inability to concentrate, loss of appetite, headache and insomnia, constitute a clearly defined picture of the beginning of poisoning. These symptoms may develop over a period of several days, or over a period of a few weeks. The insidious onset of such rather minor symptoms is a distinct feature, and they serve as a warning of the severer symptoms which may follow unless the individual is removed from exposure to the poison. Owing to their insidious onset and mild character, these minor symptoms are readily overlooked.

Severer symptoms consist of an increase of constipation, nausea and vomiting, and, in addition, gas in the stomach, generalized abdominal pain, dizziness and very slight jaundice. Such disturbances may appear suddenly, but this is unusual. Still more advanced symptoms occurring with increase of jaundice are those of cholemia, which occur associated with severe necrosis of the liver cells, very similar to those of acute yellow atrophy. No other important pathologic change has been reported.

Besides jaundice, which may become moderate in degree, the important physical signs which develop relatively late, consist chiefly of an occasional palpable and tender liver, general abdominal tenderness, pallor and loss of weight.

Immediately following removal from exposure, the symptoms do not necessarily subside but not infrequently increase for a few days. If the symptoms are of the very mildest degree, they may disappear within two or three days, even without removal from exposure. Jaundice, even though not severe, when it is once established may persist for several weeks or even months before disappearing.

There were no severe cases of tetrachlorethane poisoning among the sixty-eight employees of the artificial silk plant whom we studied during a period of five months. Twenty of these were women and were practically not exposed to the poison. The others were men exposed to a greater or lesser degree at one time or another. Among them were twelve who showed symptoms best interpreted as very mild preliminary symptoms of poisoning which persisted for a few days only. Their symptoms consisted of an abnormal sense of fatigue, irritability, constipation and headache. There were nine others who showed more definite symptoms of poisoning. Two of these were moderately sick, but not to a degree to be considered serious or alarming, and not at any time sick enough to warrant their going to bed.

In all, 275 critical Wright stained blood smear examinations of the white cells, red cells and platelets were made on sixty-eight employees. Sixty white cell counts (thirty-seven persons) and forty-four red cell counts (thirty persons) and Tallquist hemoglobin determinations were made.[10] A few other observations on the blood were made but yielded no significant information.

The only reference we have found in the literature to the blood in tetrachlorethane poisoning is by Wilcox,[4] who merely states that "the jaundice is hepatogenous, not hemolytic, and that no appreciable anemia or changes in the red blood corpuscles occur."

The blood of certain employees whom we have studied showed distinct abnormalities, the most important alteration from normal being an increase of the large mononuclear cells.[11]

Nearly all of the twenty-five persons whose blood showed this change to a definite degree, had or soon developed, especially if there was a progressive increase of these cells, some symptoms attributable to poisoning. On the other hand, none of the twenty-one employees who had symptoms due to tetrachlorethane failed to show increases of the large mononuclear cells, which often formed over 30 per cent. of the leukocytes. Other less marked and less significant changes have been found by us in the blood of persons poisoned by this chemical.

Table 1 consists of an analysis of a typical case of poisoning. It shows the progression of symptoms eventuating in jaundice which remained for several weeks after the other symptoms had disappeared. The table also shows that as the symptoms increase, progressive alterations in the blood develop, which returns toward normal as the symptoms subside. The blood changes, particularly, consist of the following features: (1) The progressive increase of the large mononuclears; (2) the progressive increase of young large mononuclears, some formed and some broken; (3) the somewhat elevated white count; (4) the slight but progressive anemia, and (5) the slight increase of platelets.

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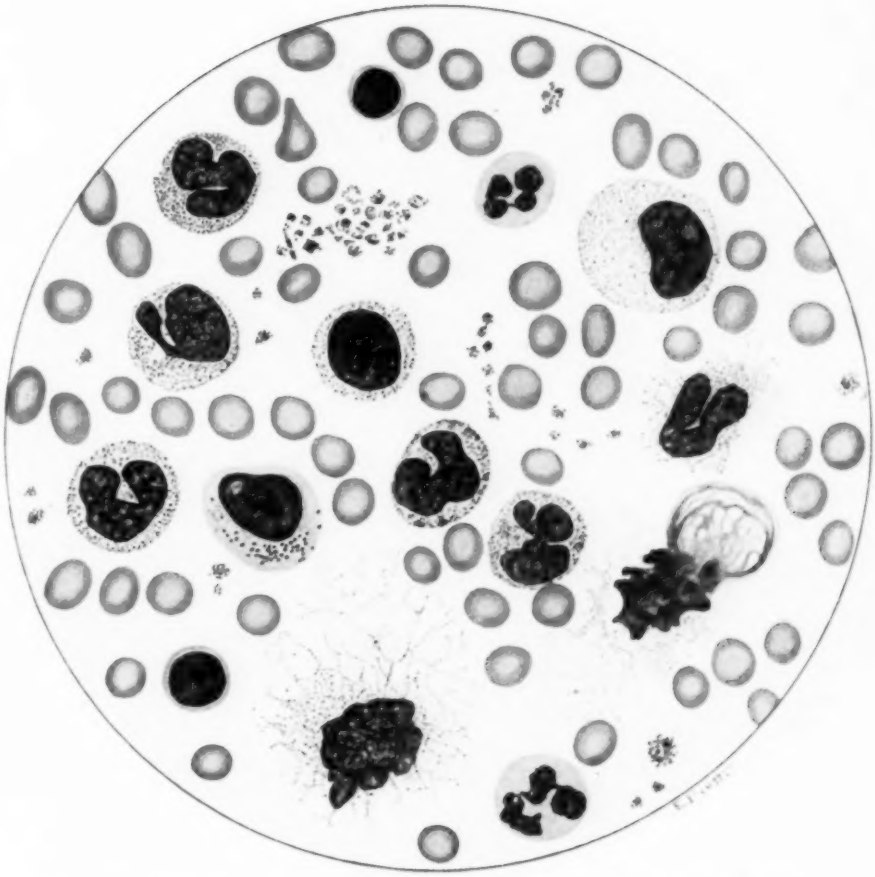
10. It is a pleasure to acknowledge the technical assistance given by Miss Margaret Weld.

11. In this paper, the term large mononuclear cells (Mallory's endothelial leukocyte) refer to those classically twice as large as a polymorphonuclear neutrophil, which are often considered to originate in the bone marrow and from endothelium to which the inappropriate term of transitional cell has been applied; especially to the more mature form with the idented nucleus. These cells are very similar to those large mononuclear cells that probably originate in lymphatic tissue, but they are usually larger, more sharply defined, more granular and stain more distinctly than the large mononuclear cells of lymphatic origin. It is quite possible that owing to the liver pathology of tetrachlorethane poisoning that the large mononuclear cells in these poisoned individuals have come from the endothelium of the liver as well as from the marrow. Both Dr. C. H. Bunting and Dr. J. H. Wright have been kind enough to examine some of the preparations and agree that the cells are of the type referred to.



The blood of a case of tetrachlorethane poisoning, stained with Wright's stain. The white cells occurred in an actual field under 570 magnifications. The drawing was made by aid of a camera lucida under 1,425 magnifications. Seven large mononuclears are present; five mature ones (transitional cells) with indented nuclei and two immature, without definite indentation of their nuclei. The cell in the lower left hand quadrant with reddish granules in the protoplasm is an atypical large lymphocyte. Two normal small lymphocytes and two normal polymorphonuclear neutrophils are shown, and three broken white cells. The larger broken cell in the lower right hand quadrant is especially characteristic.

Illustrating Article by George R. Minot, M.D., and Lawrence W. Smith, M.D.,
Archives of Internal Medicine, December, 1921

The typical blood picture is shown in the accompanying colored plate.

All of the sixty-eight persons studied have been placed into three groups, as shown in Table 2, dependent, on the one hand, on the number of large mononuclear cells in the blood, and on the other on the symptoms that occur. In this table, the figures and data shown represent an average obtained at the time that the large mononuclear counts were the highest in each case.

TABLE 1.—ANALYSIS OF A TYPICAL CASE OF TETRACHLORETHANE POISONING

Date	W. B. C. in Thousands	Per Cent. of					Broken W. B. C. per 10 Formed W. B. C.	R. B. C. in Millions	Red Cells *				Platelets †	Symptoms ‡
		Polymorphonuclear neutrophils	Lymphocytes	Large Mononuclears	Eosinophils	Basophils			Achromia	Anisocytosis	Poikilocytosis	Polychromatophilia		
Jan. 2	9.0	59	23	6	2	0	5	5.0	0	0	0	0	N	0
Feb. 18	8.5	56	31	13	0	0	4	...	—	—	—	—	..	0
Apr. 20	11.2	50	30	20	0	0	8	4.9	+	0	0	0	N	0
May 1	12.0	45	25	29	1	0	22	...	+	+	0	0	+	+
May 13	15.6	39	20	40	1	0	31	4.7	+	+	+	+	+	++§
May 16	15.2	43	22	35	0	0	26	...	++	++*	+	++	++	+++
May 23	11.4	45	29	25	1	0	18	4.7	..	..	—	—	..	0¶
June 6	10.6	50	38	12	0	0	7	4.7	+	+	0	0	+	0

* Red Cells: +, indicative of earliest recognizable changes—very slight achromia, just distinguishable variation in size or shape and one polychromatophilic cell per 10-12 oil immersion fields; ++, moderate achromia, definite but slight variation in size and shape, one polychromatophilic cell per 4-5 oil immersion fields.

† Platelets: +, very slight increase in numbers; ++, moderate increase in numbers; N, normal.

‡ Symptoms: degree indicated by + signs: +, abnormal fatigue, discontent, constipation, headache; ++, a greater degree of above symptoms, coupled with insomnia and irritability; +++, further increase of above symptoms with addition of anorexia, nausea, vomiting and slight jaundice.

§ Taken off work.

¶ Jaundice still present, no subjective symptoms.

Group I consists of all employees, twenty-five in number, who showed an increase of large mononuclear cells above 12 per cent. in a differential count of not less than 200 white cells. Twelve per cent. has been chosen rather arbitrarily but chiefly because of the fact that 10 per cent. of large mononuclears may occur in the absence of any clearly recognized pathology, and this number of these cells occurred in several people in the other groups. All of the twenty-five persons in Group I manifested clinical symptoms of poisoning at one time or another, except four. These four persons have been placed in a subgroup (labelled B in the table) and will be discussed later.

Group II consists of twenty-three male employees whose large mononuclear cells remained below 12 per cent. These men showed no symptoms of poisoning in spite of exposure to tetrachlorethane, to essentially the same degree as those placed in Group I.

In Group III are twenty women whose large mononuclear cells were below 12 per cent. and who had no symptoms of poisoning. They serve fairly well as a control group as they had almost no exposure to the poison.

Groups II and III require no further comment as neither symptoms nor significant blood abnormalities occurred.

The pathologic increase of the large mononuclear cells, together with other blood changes which occurred in the cases of Group I, are to be interpreted critically. The typical blood changes that occurred in the subjects placed in this group have been shown in Table 1. The typical case shows the large mononuclears rising progressively from approximately 10 to 40 per cent. over a period of from four to eight

TABLE 2.—Summary of Blood Findings in Sixty-Eight Tetrachlorethane Workers

	Number of Cases	W. B. C. in Thousands†	Per Cent. of					Broken W. B. C. per 100 Formed W. B. C.	R. B. C. in Millions†	Red Cell Abnormalities‡	Platelets	Symptoms§
			Polymorphonuclear neutrophils	Lymphocytes	Large Mononuclears	Eosinophils	Basophils					
Group 1a	21	12.7	40.0	30.5	26.5	2.5	0.5	25	4.4	++	+	+
Group 1b	4	10.2	41.0	35.5	22.0	1.0	0.5	8	4.9	0	+	0
Group 2	23	10.3	82.5	27.0	8.0	1.5	1.0	5	5.0	0	N	0
Group 3	20	10.2	60.0	29.0	9.0	1.5	0.5	5	4.3	+	N	0

* The figures and data given represent an average obtained at the time the large mononuclear cells were highest or near their height in each instance. Group 1—Composed of individuals whose large mononuclears were over 12 per cent.; a, with symptoms due to tetrachlorethane; b, without symptoms due to tetrachlorethane. Group 2—Composed of men, and Group 3 of women, whose large mononuclears were less than 12 per cent.

† Representative average counts; entire group not always included.

‡ +, indicative of the very slightest definite red cell abnormality, such as due to a very mild degree of secondary anemia from any cause, and as often found in the women employes; ++, indicates a rather greater degree of red cell abnormality, such as referred to in the legend of Table 1.

§ + means the presence of symptoms due to tetrachlorethane, and 0 that there were no such symptoms.

weeks, at which time preliminary symptoms of poisoning occur. Four subjects developed over 40 per cent. of large mononuclears, the highest count recorded being 56 per cent. The nine more severely poisoned subjects had usually, but not always, a slightly higher percentage of large mononuclears than the twelve very mildly poisoned workmen. In a typical case, though the symptoms of poisoning may progress over a period of a few days, there occurs no further increase of the large mononuclear cells. These cells gradually fell from the vicinity of 40 per cent. to a level of about 12 per cent. in from three to six weeks, while if they rose to only about 25 per cent., they fell in a shorter period of time. Their diminution is nearly always to be regarded as

a desirable sign, but, perhaps, this may not always be the case, as will be referred to later. Sixteen of the members of Group I were of the typical sort. However, our data shows that there may be marked variation from the typical case which would appear to be somewhat dependent on the persons resistance to the poison, and to the amount of exposure to it. The worker may show the same progression of blood changes and symptoms, but develop the blood changes over a period of less than two weeks instead of over from four to eight weeks. This is unusual and occurred in only one instance. Again, an individual may have over a period of months a relatively high level of his large mononuclears (from 10 to 20 per cent.) and then suddenly symptoms will develop coincident with a rapid rise of the large mononuclears. This may occur, as it did in one case, without realizing that any increased exposure to the poison had occurred, or, as occurred in another case, a rapid rise from 10 to 40 per cent. occurred, coincident with the acute development of symptoms due to increased exposure to the poison. In such an instance, the symptoms may develop too rapidly to be foretold by the usual routine blood examination. However, such cases show the characteristic blood picture, which returns to normal in the usual manner.

From observations of two persons developing an acute respiratory infection it was apparent that an intercurrent infection might lower the resistance to the poison. This was evidenced by the fact that their mononuclears rose in about twenty-four hours from about 10 per cent. to approximaely 40 per cent. Symptoms believed to be dependent on the poison then developed which were sufficiently ill defined to be plausibly explained as due to the infection, as similarly the blood picture might be interpreted. Coincident with removal from the poison, and with subsidence of the infection, the mononuclear count fell somewhat more rapidly than was usual in the typical case.

In spite of these variations from the typical case, it is to be borne in mind that, as a rule, the insiduous progressive onset of poisoning is the commonest form, the one to guard against and the one in which symptoms can be foretold from the blood changes.

The fact that the occurrence of clinical poisoning can often be foretold by the blood from something more than an increased percentage of large mononuclear cells, must be borne in mind. It may be foretold by progressive increases of these cells, together with changes in their character and other blood features yet to be commented on.

An increase of large mononuclears, on the average as great as occurred in the presence of symptoms, occurred in a few cases some months before symptoms of poisoning developed; though before and after the appearance of such symptoms there was a progressive increase

of the cells as well as changes in their character. This indicates that any employee carrying an abnormally high mononuclear count is to be regarded as potentially poisoned and may at any time develop clinical symptoms.

Four men, as previously noted, those of Group I b, showed an increased percentage of large mononuclears without developing symptoms of poisoning. Two of these were men about 45 years of age, who had been exposed to the poison upward of a year, and who showed an increased percentage of their large mononuclear cells for three months. The two others were boys about 17 years of age, who had been exposed to tetrachlorethane for from twenty-four to forty-eight hours. The increase of the large mononuclears in the older men may be explained on the ground of a constant chronic irritation by tetrachlorethane—a calling out of the first line of defense. This is further suggested by the fact that when these men changed their work to a place of less exposure, their large mononuclears became markedly reduced over a period of four months. The case of the boys, whose large mononuclear count fell nearly as rapidly as it rose, although they continued at work, we may easily assume as being due to a reaction to the substance. It would seem that as their bodies found they could functionate without the need of so sharp a reaction to tetrachlorethane, the count fell.

A high mononuclear count appears to be the earliest sign of a reaction to tetrachlorethane. The mere fact that there is an increase of the large mononuclears is not sufficient evidence to advise that a man be employed in different work. A high count alone, which does not become progressively higher has not nearly the same significance as a count rising slowly, particularly over a relatively short period of time, except apparently, when persons are first exposed to the poison.

Besides the fact that a progressive increase of large mononuclears is more significant of a deleterious effect of tetrachlorethane than a stationary level of these cells, there is another alteration in the large mononuclears that is significant in indicating the clinical prognosis. This is referable to their detailed character. It was found that there was a rather distinct relationship between the youth of the large mononuclears and the degree of clinical poisoning. With an increase of large mononuclears, the greater the number of young large mononuclear cells, the sooner there developed clinical evidence of poisoning. While if symptoms were present and increased, there occurred an increase in the number of young, large mononuclears.

We consider that the younger large mononuclear cells are differentiated from the older in the following ways: The nucleus of younger cells is oval or round and usually less homogeneous in contrast to the indented or lobed rather dense nucleus of the adult cell. The more

youthful cells are usually of a different size than the more mature ones; they are sometimes smaller, with the cytoplasm relatively less in amount in proportion to the nucleus than in the adult cell, but on the contrary, are usually larger with a relatively large amount of cytoplasm. It is characteristic for the cytoplasm of the younger forms to be more basophilic and contain fewer azuriphil granules. A certain amount of difficulty was experienced in making accurate differential counts in these cases, dependent on the great variation in the character of these cells, as indicated above. At times, differentiation from derivatives of the lymphoid system is perhaps impossible. The use of Goodpasture's modification of Graham's oxydase stain, which stains the granules of cells of myelogenous origin, and not those of lymphocytes, was found of assistance as a supplement to the Wright's stain.

An increased fragility to mechanical injury (as from pressure of a cover glass) of white cells may be regarded as evidence of youth. Cells that have become broken cannot be classified in a differential count, but when one can trace a series of cells from those that are intact to those that are broken, one may conclude that the majority of such broken cells are of the type to which they can be traced. In our preparations the majority of the broken or fragile white cells could be interpreted best as large mononuclears. The frequency of these disintegrated cells has been indicated in the tables. They were found quite consistently in increasingly greater numbers as the clinical symptoms appeared or progressed, and were associated with increases of large mononuclear cells showing the other signs of youth. The increases of these fragile forms occurred with too great regularity to be considered purely due to careless technic, though, of course, a few such cells, some of which are probably adult cells, will occur in practically any blood smear.

The numbers of these distorted cells, together with the number of other youthful large mononuclears is to be regarded as a very definite factor in forming a prognosis. The more there were of such cells, indicating increased activity of the tissue from which they are formed, the sooner definite symptoms occurred or more serious symptoms developed. It was common to find from three to seven days before symptoms developed, from ten to twenty broken cells to one hundred formed white cells. With the presence of definite symptoms they increased, on the average to about forty per 100 formed white cells, while in some of the more marked and more acute cases of poisoning they reached to over 100 per 100 formed white cells. No case of poisoning showed less than fifteen fragile cells to 100 formed white cells. Likewise, the formed large mononuclears in the poisoned individual had very varying characters, some were very young and others were mature, with all variations between these extremes. In contrast to this picture, those four persons who did not develop symp-

toms, and those poisoned persons who had high large mononuclear counts, some weeks or even months before poisoning occurred, showed at such times usually only about ten fragile to 100 formed white cells. There was also little variation in the character of their mononuclears, which were particularly of the more adult forms. In other words, when symptoms of poisoning occurred there was much greater activity of formation of the large mononuclears than when symptoms did not occur, even though they might be increased in numbers, indicating a reaction to tetrachlorethane.

It is evident that increases of the large mononuclear cells indicate a reaction to tetrachlorethane and appear to be an early sign of poisoning which may occur before clinical symptoms are apparent, while the youth of these cells, as told by their histologic appearance, is a sign that indicates somewhat the degree of poisoning. These signs are of considerable importance in deciding whether a man should be laid off from work exposing him to tetrachlorethane, and, if so, for how long. Before formulating rules as to how blood examinations may be used to prevent poisoning and for its diagnosis, it is desirable to describe the other less important alterations of the blood that were observed in these workers. These other blood changes are referable to the total leukocyte count, further alteration in the differential leukocyte count, the red cells and platelets.

Accompanying the increase of large mononuclears, there occurred a slight, absolute increase of the leukocytes, never above 22,000 per cm. and usually about 12,000 per cm. The higher counts were apt to be found coincident with the greater increases of the large mononuclears and when they showed the greater histologic changes from normal. Among twenty-three individuals exposed to tetrachlorethane, but presenting no signs or symptoms of poisoning ,and who had no other blood changes, the white count averaged 10,300. These observations suggest that anyone who comes in contact with tetrachlorethane is very apt to have a slightly elevated leukocyte count, and thus this chemical tends to cause an increase of the total number of white cells.

Alteration in the differential count, other than alteration in the large mononuclears, is of relatively slight importance. Often there was found an initial relative decrease of the polymorphonuclears, without particular fluctuation of the lymphocytes, coincident with the increase of large mononuclears. With a decrease in the percentage of large mononuclears, the lymphocytes frequently rose more rapidly than did the polymorphonuclears, often reaching a percentage higher than that preceding the initial changes due to tetrachlorethane. It is our impression that should a person become distinctly severely poisoned (one example of which we have seen, but who was not in the group of workers we have especially studied) that the large mononuclear

cells may fall, the defensive reaction having been overcome, and one may then find a definite lymphocytosis. Thus, if the clinical symptoms of poisoning were progressive, and the large mononuclear count was falling, while the lymphocytes were rising, it should not be necessarily interpreted that the individual was getting better, but that he was getting worse. In morphology, the lymphocytes seemed to be for the most part normal. In some cases, particularly with an increase in their numbers, there was a somewhat increased percentage of large lymphocytes, some of which were atypical.

Besides alterations in the percentage of polymorphonuclear neutrophils referred to above, the only other abnormality they presented was that at times young forms were found in the peripheral blood. Young forms in rather small numbers were especially seen when there was evidence of considerable heightened activity of the formation of large mononuclears.

No definite variation from normal was found in the polymorphonuclear eosinophils or basophils.

The abnormalities of the red cells that were observed were distinctly of secondary interest and importance as compared with the abnormalities in the white cells. The average red count in eleven men (twenty-five counts (with symptoms of poisoning, was 4,400,000 (varying from 3,900,000 to 5,200,000), while in ten men (ten counts) who had no increase of their large mononuclears, and who had no symptoms, the average red count was 4,900,000 (varying from 4,700,000 to 5,200,000). The average count among nine women (nine counts) who had no symptoms of poisoning, and who for the most part were typically pale factory girls, was 4,300,000 (varying from 4,100,000 to 4,600,000). No accurate hemoglobin determinations were made. By the Tallquist scale, it was apparent that there was a slight reduction of hemoglobin that roughly paralleled the red counts. Abnormalities of the histology of the red cells in the poisoned cases were more evident than the variation from normal of the red count and hemoglobin. The amount of achromia, variation in size and shape and polychromatophilia, that was observed in the average case has been indicated in the tables. There was no evidence of abnormal fragmentation of the red cells, such as occurs in trinitrotoluene poisoning, to suggest that any important degree of blood destruction occurred in tetrachlorethane poisoning. In no case, were the abnormalities of the red cells present to more than a slight, yet definite, degree. The abnormalities were distinctly more apparent in the men developing poisoning, whose red counts, in turn, were lower than those of the men who did not develop poisoning, yet higher than in the women who were not poisoned.

All the instances of this simple anemia, unexplained by some other cause than due to tetrachlorethane, and as particularly told by the

histology of the red cells, developed in cases that showed increases of large mononuclears or clinical symptoms of poisoning. However, anemia did not develop in every case of poisoning. The red cell changes were somewhat more marked in the more chronic and more severely poisoned cases. From our data it appears that the anemia is slowly progressive, especially when symptoms persist or with recurrence of poisoning, but it does not become serious. In any given case, the amount of red cell abnormality alone would be of very slight importance in judging the state of the worker. However, the presence of red cell abnormality is to be regarded as an undesirable finding, and particularly when present with the more important white cell abnormalities, it is to be considered an additional sign to indicate that the worker should be removed from the poison. It is also probably wise to consider that the poisoned individual with anemia should remain longer from exposure to tetrachlorethane than one without anemia, and that persons with anemia should not be exposed to this substance.

The blood platelets as estimated from fixed smears were frequently found slightly increased above normal. As might be expected, their increase was usually more apparent in those cases showing distinct abnormalities of the large mononuclears and changes in the red cells, than in those with lesser changes in these elements. Abnormally large platelets were rather frequently found in cases showing other abnormal blood histology.

From this study of the blood of tetrachlorethane workers the hopes that blood examination might be of value in regulating the employment of those exposed to this poison, have been rather definitely fulfilled.

On the basis of the correlated study of the clinical picture and the blood, the following recommendations regarding blood examination are made for the prevention and diagnosis of poisoning by tetrachlorethane. These recommendations apply when the substance is used under such satisfactory conditions as were observed during our investigation.

A routine blood examination should be made before a person is accepted for work. This will particularly establish his normal level of large mononuclear cells and will determine the presence or absence of any anemia. As anemia probably favors the development of poisoning, if there is any definite degree of it the persons had best be rejected.

A critical examination of a stained blood smear should be made on each new employee at the end of the first and second week, and then once every three or four weeks during the first six months of his exposure to tetrachlorethane. After the first six months, less frequent examination of the blood is necessary. It appears that a given individual is much more likely to develop evidence of poisoning during

the first six months of his exposure. This is substantiated by the fact that in the subjects examined, seventeen cases of poisoning occurred among the men employed for less than six months, while only four cases occurred in a group of essentially the same number who had been employed for more than six months. A new employee may have an initial reaction to the poison. In the event of his being distinctly susceptible, the blood picture may progress from that point. In the event of his being less susceptible, his initial mononuclear rise subsides and probably some tolerance is established.

If the routine blood examination reveals the large mononuclear cells above 12 per cent., more frequent examination is indicated. The frequency of such examinations will depend on the relative rate of increase of the large mononuclear cells together with their numbers showing signs of youth, as well as the presence of even the most trifling clinical symptoms.

Any individual, with a percentage of large mononuclear cells of more than twelve must be considered, for the purposes of diagnosis and prognosis, potentially as a poison case, because an increase of the large mononuclear cells seems to be the first sign of a reaction to tetrachlorethane. However, this arbitrary figure of 12 per cent. cannot be utilized alone in regulating his employment, except ideally and impracticably. From the point of view of the employer, such regulation would result in serious economic loss, and from the outlook of the employee injustice would be done. Also, it is evident that no recognizable harm comes to the employee who is allowed to reach the point of developing the very earliest clinical symptoms of poisoning.

We have already noted that the large mononuclears in the twelve mildest cases were often as high as in the nine more severe cases, who were removed from work. However, in these more severe cases the presence of larger numbers of younger mononuclear cells and broken cells was very much more constant than in the twelve milder cases. The determining factor in the removal of the nine men was not only that the blood changes were more marked but that the clinical symptoms were more marked. In both instances, it was on account of the blood examination that these persons came under critical observation; some, however, were allowed to develop a greater degree of poisoning than we now feel is desirable to permit. Of the nine severer cases, all but the two acute ones could have been removed from work sooner than they were, and should have been from the evidence of poisoning obtained from the blood as well as by symptoms.

The regulation of employment, therefore, from the point of view of the blood findings has to be based particularly both on the relative increase of the large mononuclear cells over a definite period of time and on the number of the young and fragile forms.

It may be stated that a progressive increase of large mononuclear cells alone does not call for removal of an individual from work, but calls for his close observation. If the slightest clinical symptoms develop, it is desirable to remove him from exposure. It is permissible, however, to allow him to continue at work for a few days unless his symptoms increase in the least, or his blood picture becomes more abnormal, as particularly evidenced by an increase of the formed and broken young large mononuclears. Any person having symptoms, even if very slight, for more than a few days, with abnormalities of the blood, should be excused from work. An increase of large mononuclear cells, from 12 to 20 per cent., or from 20 to 40 per cent., for a period of two or three weeks, is to be considered as of much more significance than a similar increase for a period of from two to three months.

In the same way that the blood serves as an important guide to indicate when to take an employee off work, so it serves in regulating his return. No person should return as long as any clinical symptoms persist, with the possible exception of a very slight and subsiding jaundice. If the subjective symptoms have subsided and the large mononuclear cells have been reduced by at least 50 per cent. from their highest point, then, even, perhaps, in the presence of slight jaundice, if none of the younger forms occur in the blood, a man may be allowed to return to work, provided he is kept under the strictest observation. The absolute percentage value of the large mononuclear cells is of less importance; that is, it does not appear to be absolutely necessary for the large mononuclear cells to return to 12 per cent. or less before allowing a person to resume work. The presence of definite anemia is a contraindication to returning to work, and is usually sufficient evidence to advise a change of occupation.

The period of time that the poisoned subjects were removed from exposure varied from a few days to six or even eight weeks. In general, the sooner a man was removed from work after definite blood changes and slight symptoms occurred, the shorter was the time lost.

The reason that these persons should be watched particularly carefully on returning to work after poisoning, is because there seems to be a tendency for those who have become poisoned once to become poisoned again and usually relatively more rapidly than before. If an individual becomes poisoned twice within a few weeks, or several times some months apart, it is wise that he should change his employment. It was found that with the recurrence of poisoning the blood changes were usually more severe and more rapid.[12] As stated, it may be desirable to supplement the routine blood examination with others,

12. Instances of recurrent poisoning are not included in the previously referred to twenty-one cases of poisoning.

according to the exigencies of the case. These more frequent tests may be made purely because the blood has been abnormal, or because some symptoms have occurred. It is to be clearly understood that every employee developing any symptoms, no matter how trivial, which could in any way be interpreted as due to tetrachlorethane, should have a critical blood examination. Under such conditions the blood will materially aid in the differential diagnosis of the cause of the symptoms. If the typical blood changes described as due to tetrachlorethane are present, the symptoms had best be credited to the poison; while if no increase of large mononuclears occurs, the symptoms can be attributed to some other cause. In this connection it is desirable to note that occasionally certain acute infections and other conditions may cause a considerable increase of the large mononuclears. However, confusion in the diagnosis between tetrachlorethane poisoning and conditions that occasionally give a blood picture simulating that due to tetrachlorethane, must be rare.

We feel that blood examination utilized in the manner outlined above is the most important single criterion we have for indicating the onset of poisoning by tetrachlorethane or its initial symptoms. It is concrete and the important changes that take place are constant. This is in contrast to the very earliest symptoms of poisoning, which are vague and indefinite. Such symptoms, however, are shown to be quite definitely due to poisoning when present with the blood changes described. During our study we have been able to prophesy frequently from the blood some days before clinical symptoms occurred that such symptoms would appear. The blood changes were found to be invariably the first symptoms or signs to appear and other than jaundice, were the last to disappear. However, blood examination is not infallible in detecting poisoning before clinical symptoms develop, because occasionally, from undue exposure, symptoms may develop so rapidly that they could not be anticipated from routine blood examinations.

The acute development of even slight symptoms may be due to a relatively sudden greater exposure to the poison or to the action of some factor not clearly understood, as a lowered resistance from infection. However, such cases will show the typical blood changes so that diagnostically the blood is always helpful.

One should most emphatically not rely on blood examinations alone to keep the health of these employees at its best. It aids to detect the early, often apparently insignificant, symptoms due to poisoning, and serves as an absolute check on them. Blood examination should be utilized as a valuable method to aid in the prevention of serious poisoning, and in the diagnosis and prognosis of poisoning. However, proper clinical supervision of those exposed to tetrachlorethane, as outlined by Dr. Parmenter, is of the utmost importance. If blood

examination is used intelligently, it can aid to reduce materially the time lost from work, for early removal from exposure may reduce the time out to less than a week; while cases that go on to the development of jaundice, usually require at least a month.

It is only by careful observation, at least every few days, together with a clear conception of the initial symptomatology of the poisoning, and with utilization and proper interpretation of blood examinations, that poisoning can be kept at a minimum. Under such circumstances, carried out by Drs. Parmenter and Smith, the number of working days lost due to poisoning in this artificial silk plant, has been reduced for the five months preceeding March 1, 1921, by about 40 per cent. below what the number was for the five motnhs beginning Jan. 1, 1920, when the original investigation reported here was conducted.

SUMMARY

1. A study of the blood of sixty-eight persons exposed to a greater or lesser degree to tetrachlorethane, indicates that blood examination is of value in the prevention of tetrachlorethane poisoning and in the diagnosis and prognosis of poisoning by this substance.

2. All persons presenting clinical symptoms of tetrachlorethane poisoning (twenty-one in number) showed characteristic blood abnormalities. The blood changes usually can be observed before clinical symptoms develop.

3. The blood abnormalities include (a) a progressive increase of large mononuclear cells, often reaching 40 per cent. This is the most important change. (b) The appearance of many immature large mononuclears. (c) A slight elevation in the white count. (d) A progressive but slight anemia. (e) A slight increase in the number of platelets.

4. A percentage of large mononuclear white cells above 12 is the first sign of a reaction to tetrachlorethane, and is a signal for close observation of that person. All persons with such a picture do not necessarily develop clinical symptoms of poisoning.

5. The presence of a considerable number of young large mononuclear cells, some formed and many broken, is to be considered as indicating a severer condition than when the same number of more mature large mononuclears are present.

6. A consideration has been given to the utilization of blood examinations in connection with careful clinical observations in the regulation of employment of those exposed to tetrachlorethane.

THE EFFECT OF THE EXTRACT OF THE POSTERIOR LOBE OF THE PITUITARY ON BASAL METABOLISM IN NORMAL INDIVIDUALS AND IN THOSE WITH ENDOCRINE DISTURBANCES *

C. A. McKINLAY, M.D.
MINNEAPOLIS

That there is an interrelation of the glands of internal secretion is well known. Rowntree [1] states that where life is, metabolism is, and regulating it are the endocrine glands. Kestner [2] states that all endocrine glands are closely related and that the most intimate relation exists between the thyroid and hypophysis. Engelbach [3] mentions as a fact that the hypothyroid state is frequently associated with hypopituitarism. Peritz [4] thinks that the intensive growth in length of bones which is sometimes found in exophthalmic goiter may be ascribed to a functional disturbance of the hypophysis. Holmgreen [5] mentions that exophthalmic goiter patients in youth may show accelerated growth in height. Friedman [6] believes that there may be a mild overactivity of the hypophysis in exophthalmic goiter and a mild underactivity in myxedema.

Numerous growth and feeding experiments give evidence of the relationship between the endocrine glands. Rogowitsch [7] concluded that the changes in the hypertrophied hypophysis which follow thyroidectomy in mammals is indicative of a gland of low function. Fry [8] points out that the histology of the hypophysis in exophthalmic goiter corresponds to a gland of high activity; in myxedema to one of low activity. Larson [9] has fed the anterior lobe of the hypophysis to thyroidectomized

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rats and finds that it has a beneficial effect on their growth. Kojima [10] found in rats after thyroidectomy hypophyseal changes indicative of a gland of low activity. Hart [11] noted atrophy of the thyroid in tadpoles fed with thymus; he states that monoglandular disturbance is often followed by changes in the other organs of the endocrine system and that what would appear to be monoglandular diseases are often polyglandular.

Certain tests to aid in diagnosis have been described which have their rationale in endocrine interrelationship. According to Goetsch,[12] who revived the work of Eppinger and Hess,[13] the hypersensitiveness of the sympathetic nervous system to epinephrin has been made the basis of his epinephrin test. Ascoli and Fagiuoli [14] describe a test consisting of subcutaneous injection of pituitary extract with positive local reaction strengthened in affections of the pituitary body. The reaction is often entirely dissociated from that to adrenalin which they also describe. Porak [15] found that injection of the extract of the posterior lobe of the hypophysis had much more effect on the blood pressure of myxedematous patients than of normal subjects as shown by sudden and prolonged fall of tension. The observation was also made that injection of thyroid extract in normal subjects causes lessened blood pressure, but not in individuals with myxedema. Porak thinks that it is possible by these tests to confirm or exclude hypothyroidism in complex syndromes. Boothby and Sandiford [16] have shown that epinephrin causes an increased heat production in the body, and conclude that there is no apparent relationship between cases positive to the Goetsch test and hyperthyroid states as measured by their basal metabolic rates. Cushing [17] states that in the early stages of acromegaly there is a definite increase in metabolism, whereas in the reverse states the rate averages at least twenty points below normal. Engelbach [3] seems to conclude that there is usually increased basal metabolism in hyperpituitarism. Snell, Ford, and Rowntree [1] state that in a small series of cases no profound or lasting effect on basal metabolism resulted from

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the subcutaneous use of the extract of the posterior lobe of hypophysis. Their investigation did not include its immediate effect when used subcutaneously.

To determine what influence the extract of the posterior lobe of the hypophysis when used subcutaneously has on heat production in normal persons and in those with endocrine disorders, chiefly of the thyroid and pituitary, has been an object in this study. Whether thyroxin,[18] the active principle of the thyroid gland, and pituitary extract have any interrelated effect on basal metabolism has been a point of extreme interest.

Material and Methods Used.—The gasometer method of obtaining the basal metabolic rate has been used and air analysis was made with the Haldane apparatus. The usual precautions have been observed to have the patient in the postabsorbtive stage; that is; determinations were made in the morning fourteen hours after any food intake. The patients have been subjected to a twenty minute rest period while lying down. After such preparation this routine method has been employed: (1) Collection of air for the initial determination of the basal metabolic rate; (2) followed within ten minutes by a subcutaneous injection of pituitary extract; (3) collection of expired air started twelve minutes after injection. The preparation used has been the extract of the posterior lobe and pars intermedia, approximately 1 c.c. in amount, except as otherwise indicated in the text. The collection of the expired air has averaged between eight and ten minutes. Especial care has been taken during the experiments to control all extraneous factors that might alter the patient's basal metabolism during the routine procedure. In view of increased restlessness which is sometimes apparent after protracted rest periods, a control series has been included.

This group consists of five normal persons who were subjected to the routine procedure mentioned above, except for the omission of the pituitary extract between the two determinations. In Table 1 are shown the results in which the variation in the basal metabolic rate in each individual has never been more than one per cent. in the two determinations. Such a small variation appears to be a negligible factor.

In the cases given thyroxin administration was intravenously in 10 mg. dosage. One week later, approximately at the height of the accelerating effect of thyroxin on basal metabolism, pituitary extract was administered according to the routine procedure before described, with the purpose of observing the combined physiologic effects of the two products.

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18. Kendall, E. C.: The Isolation in Crystalline Form of the Compound Containing Iodin Which Occurs in the Thyroid and its Chemical Nature and Physiological Activity, Tr. Ass. Am. Phys. **33**:420, 1915.

The individuals on whom the experiments have been performed have been grouped as follows: (1) Normal; (2) hypothyroid; (3) pituitary disorders, and (4) normal and hypothyroid cases given thyroxin. The description of cases is given under each group.

TABLE 1.—Normal Individuals Used as Controls with Two Successive Determinations of the Basal Metabolic Rate

No.	Initial Determination	Second Determination	No.	Determination Initial	Determination Second
1	−3	− 4	4	+0.5	+ 1
2	−9	−10	5	+1	+ 0
3	+1	+ 0.5			

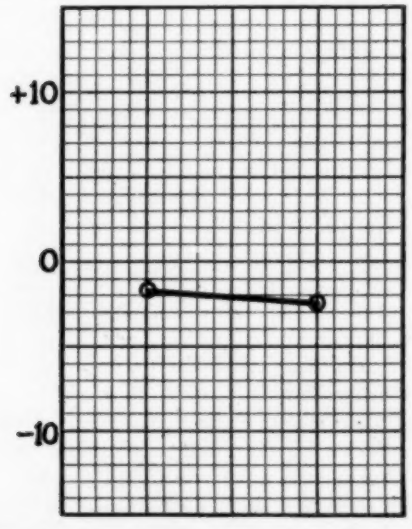

Fig. 1.—Control Group. Average of two successive determinations of basal metabolic rate without the use of pituitary extract in five normal individuals.

DISCUSSION

The normal individuals included in Group I, a majority of them students, have shown no evidence of endocrine disturbance, and their basal metabolic rates were all within normal limits. Eleven out of twelve responded with increased heat production following the use of pituitary extract. The percentile increase in basal metabolism varied from 2 to 16 and averaged 5. No pronounced effect was noted on the rate of respiration. The total ventilation was generally increased. Blood pressure determinations revealed slight systolic elevation in some

subjects; entirely absent in others. Quite marked pallor has been noted in many of the patients within twenty minutes following the use of pituitary extract. Subjectively abdominal cramps have been commonly noted.

TABLE 2.—NORMAL INDIVIDUALS GIVEN PITUITARY EXTRACT

No.	Initial Determination	Determination After Injection	Determination 20 Minutes Later
1	— 2	+ 2	....
2	+10	+17	....
3	+ 3	+ 7	....
4	+ 3	+ 7	....
5	+ 1	+ 3	....
6	—12	— 4	— 9
7	— 5	0	....
8	+ 7	+13	....
9	+ 2	+ 2	....
10	— 7	+ 9	....
11	+ 1	+ 5	....
12	—10	0	....

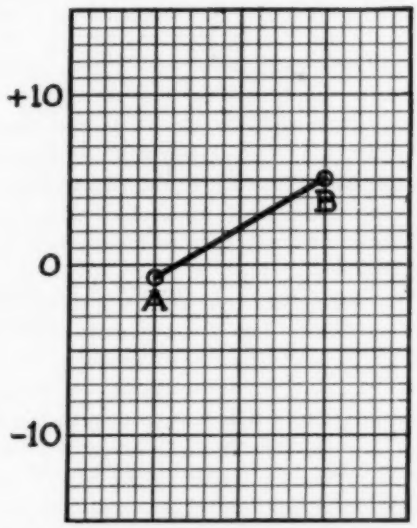

Fig. 2.—Effect of pituitary extract on twelve normal individuals; average basal metabolic rate, A=before, B=after use of pituitary extract.

Group II consists of four cases of hypothyroidism. Their response to pituitary extract is intensely interesting. Three of these are cases of myxedema whose manifestations were mild, judged by clinical signs and basal metabolism. Heat production in these cases was diminished

rather than increased. Another case of hypothyroidism developing after lobectomy showed similar response following the use of pituitary extract. In this group the subjective symptoms were less marked than in the normal individuals, no elevation of blood pressure being observed, which is in keeping with the findings of Porak.[15] In marked contrast to its accelerating influence on basal metabolism in normal individuals pituitary extract was entirely inert in a group of four subjects with hypothyroidism. It seems, then, that pituitary extract is not effective in accelerating heat production in cases with inactivity of the thyroid. This observation may be taken as evidence that there is a synergy between the thyroid and the hypophysis, if we may judge from the influence pituitary extract has on normal thyroid activity in accelerating basal metabolism. The explanation of the cause of such an interrelation is not clear at the present time and therefore demands further investigation.

TABLE 3.—Hypothyroid Patients Given Pituitary Extract

No.	Initial Determination	Determination after Pituitary Extract	No.	Initial Determination	Determination after Pituitary Extract
1	—15	—17	3	—19	—22
2	—11	—15	4	—14	—16

Group III includes three cases in which disturbed function of the hypophysis was evidenced by the development of obesity, increased sugar tolerance, subnormal temperature, and dysmenorrhea in one of them. Though in these cases basal metabolism was diminished, the thyroid was apparently normal judged by absence of signs of myxedema. In these cases, as in normal persons, pituitary extract accelerated heat production. In such relationship holds true in a larger series of cases, it is suggested that the determination of the effect of pituitary extract on basal metabolism may be used as a test to estimate in pluriglandular cases the extent, if any, of thyroid involvement. In the small series of cases observed, it seems to hold true that cases with low heat production, associated with frank thyroid disturbance, do not respond to pituitary extract while those associated rather with hypophyseal disturbance respond as do normal persons with increased basal metabolism.

Group IV consists of cases in which thyroxin was administered intravenously, followed in one week by pituitary extract subcutaneously. The normal individuals included in subdivision "A" all responded with an increase in basal metabolism which amounted to 8 per cent. This should be compared to 6 per cent. in a similar group without thyroxin. Apparently, then, in four normal individuals thyroxin has increased the accelerating influence of pituitary extract on basal metabolism. On

the other hand, two patients with myxedema, included in subdivision "B," who had likewise received thyroxin with subsequent increase in heat production, showed no response to pituitary extract. In two cases with subnormal thyroid activity pituitary extract, then, has been entirely ineffective in accelerating heat production. Such ineffectiveness persisted when the thyroid was temporarily stimulated to activity by thyroxin.

TABLE 4.—PATIENTS WITH PITUITARY DISTURBANCE GIVEN PITUITARY EXTRACT

No.	Initial Determination	Determination after Pituitary Extract	No.	Initial Determination	Determination after Pituitary Extract
1	−15	− 1	2	−12	− 9
	−23	−15	3	−14	+ 1

Whether any conclusion can be drawn from the findings that a group of normal subjects given thyroxin responded with a greater increase in basal metabolism than those without it, is doubtful. Taken, however, with other observations it suggests that there is a synergic action between pituitary extract and thyroxin and that such action depends upon a normally functioning thyroid. The experiment may, then, be interpreted to give evidence that heat production of the body is due to a balance between endocrine glands, more specifically between the thyroid and hypophysis.

TABLE 5.—PATIENTS GIVEN THYROXIN FOLLOWED ONE WEEK LATER BY PITUITARY EXTRACT

Subdivision A—Normal individuals.

No.	Initial Determination	Determination after Pituitary Extract	No.	Initial Determination	Determination after Pituitary Extract
1	+16	+18	3	+21	+29
2	+12	+20	4	+11	+24

Subdivision B—Hypothyroid Cases.

No.	Initial Determination	Determination after Pituitary Extract	No.	Initial Determination	Determination after Pituitary Extract
1	+16	+13	2	+ 9	+ 9

COMMENT

While the number of cases observed has been limited, it has been shown that in normal persons there is quite constantly increased heat production following the subcutaneous use of pituitary extract within certain time limits. In the group with hypothyroidism the evidence is strongly suggestive that there is lacking this positive response to

pituitary extract and the findings stimulate one to further observations on a larger series of cases. It is suggested that the response following pituitary extract may be used as a test to aid in the determination of the extent of thyroid involvement in pluriglandular disturbances. The evidence at hand is interpreted as indicating that there is a synergic action between thyroxin and pituitrin, the recognition of which may be of therapeutic as well as of diagnostic value.

CONCLUSIONS

1. Normal persons responded quite constantly with increased basal metabolism following the subcutaneous injection of pituitary extract.

2. In a small series of cases with hypothyroidism the basal metabolism was diminished rather than increased, which suggests that pituitary extract is effective in accelerating heat production only in the presence of a normally functioning thyroid gland.

3. In four cases with subnormal basal metabolism in which clinical evidence of myxedema was lacking and preponderance of influence of endocrine glands other than thyroid was suggested, the positive response to pituitary extract was present.

4. The increased acceleration of basal metabolism in a group of normal individuals following the subcutaneous injection of pituitary extract one week after an injection of thyroxin is interpreted as suggesting a synergic action between thyroxin and pituitary extract.

CAPILLARY POISONS AND ACIDOSIS*

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INTRODUCTION

In his admirable review of the functional activity of the capillaries and venules, Hooker [1] brings out the facts that these structures change in caliber independently of the larger vessels, that they function actively and are responsive to both chemical and nervous influences. He pictures a nervous control, maintaining a tone of the capillary beds over the body as a whole, and a chemical regulation, usually local in character and effective according to the passing need of particular tissues.

As Hooker points out the story of capillary function is far from complete. What facts are known have to do with contraction and dilatation, and the question of capillary permeability is practically untouched. In an ultimate analysis, the function of the capillaries is to allow of the passage of oxygen and nutriment from the blood to tissues and the removal of waste products from tissues to the blood. A physiologic permeability is essential, therefore, for the nutrition and activity of tissues, and the complete mechanism of dilatation, contraction and pressure changes is for the purpose of obtaining and regulating this permeability. The facts bearing on this phase of capillary function are extremely meager.

A knowledge of physiologic function is often added to materially by a study of pathologic changes and their effects. Of special importance in connection with capillary function is the study of the early stages of acute inflammation. It may be assumed that inflammation occurs only when some injurious agent introduced from without or formed from damaged cells comes in contact with an area of tissue. As MacCallum [2] points out, the first evidence of inflammation consists in a widening of the visable capillaries and the opening of new, hitherto unseen capillary areas. At this time there is an increase in the rate of blood flow. These changes are the ones usually described as following the application of any chemical irritant. Very shortly, however, the rate of flow becomes slower, with the red cells occupying the middle of the capillary channel, and plasma and leukocytes occupying the marginal borders. Obviously this change is due to some alteration

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1. Hooker: Physiol. Rev. **1**:112, 1921.
2. MacCallum: Textbook of Pathology, Ed. 2, p. 136.

in the capillary structure. Further, and probably from the beginning, a change in permeability occurs, which is demonstrable through the passage of fluid and leukocytes into the tissue.

The nature of the capillary change in inflammation is not clear. Klemensiewiez [3] believes that there is a paralysis of the capillary walls and supports this by showing that they fail to respond to nervous or direct stimulation. A simple paralysis would fail to explain the whole process, and Samuel,[4] who holds that the tissue lesions are always secondary to the vascular ones, concludes that there is primarily some unexplained but specific effect on the capillary walls. In accepting this rather vague hypothesis it is evident that the specific effect may be induced by a vast number of chemical substances whose only common character is that they are irritants. This group produces its effect when applied locally, the effect comes on promptly, and the extent of injury is proportional to the concentration of the irritant and the length of time it remains in contact with the tissue acted on. It must be admitted that although the capillary walls may be especially sensitive to the irritant, other tissues may similarly be damaged by direct action. But the fact seems clear that in acute inflammation there is primarily an injury to the capillary endothelium which manifests itself not only in change in caliber but in abnormal permeability as well.

There is another group of substances which act similarily on the capillaries when brought to them by the circulation and which, in very minute doses, produce wide spread effects. The action on the capillaries appears to be as selective as that of strychnin on the nervous system, or digitalis on the heart. These substances are classed pharmacologically as capillary poisons. The term has a wide application. It includes those substances which cause a widening or paralysis of the capillaries without inducing visible structural change. It includes also those which produce changes in caliber, accompanied or followed by structural changes. As a representative of the first group, histamin may be mentioned. This induces a wide spread but transient capillary dilatation.[5] The second group is made up of substances of such varying chemical nature as uranium, cantharidin, emetin, diptheria toxin, sepsin and gold. While many of these are irritants, this property does not explain the wide spread effects produced by minute dosage, unless one conceives a highly specific and selective irritant action. This group in its initial action produces a dilatation of capillaries. Very shortly, however, a structural damage may become apparent and constitute the main feature. While the action appears at times to be localized,

3. Klemensiewiez: Entzündung, Jena, 1908.
4. Samuel: Virchows Arch. f. path. Anat. **121**:273-396, 1890.
5. Dale and Richards: J. Physiol. **52**:110, 1918.

this, as a matter of fact, is not strictly the case, for they may act on capillaries generally. They tend, however, to have a more intense effect on one organ or tissue than on others, this effect overshadowing other, less intense ones. Thus uranium and cantharidin are often considered purely as kidney poisons and emetin as an intestinal poison. The explanation of the evident selectivity of action lies in the excretion of the poison or other factors which determine its concentration. Thus, if given by injection into the jugular vein, the lung capillaries may be the ones chiefly affected, because the poison comes to them in greatest concentration. Those excreted by the kidney produce their greatest effects here, those excreted by the intestine, on that organ. However, if these localized effects are not severe enough to cause early death, changes elsewhere can usually be detected.

Some of these poisons act much more generally than others and this is especially the case with gold salts, sepsin and diptheria toxin. If the mesentery of a frog is observed under a low power microscope, in from one half to one minute after the injection of gold-sodium chlorid,[6] new capillary fields suddenly appear, the rate of flow is rapid and then quickly slows. In mammals the veins become strongly distended and hemorrhages are numerous in the liver, spleen, kidney and intestine. With diptheria toxin [7] there is marked injection of the small vessels and wide spread destruction of capillaries with outpouring of blood. Sepsin [8] also causes wide spread hyperemia and hemorrhages. Similar effects may be obtained with emetin,[9] but these are confined to the stomach and intestine, as is the case with colchicine. Such extreme effects as these must, of course, abolish entirely the function of the capillaries involved.

If it is true that these poisons, when their action is well developed, produce structural injury and impaired permeability of the capillaries, it follows that definite effects from these changes should be obtainable and measurable. Among these effects would be departures from the normal metabolism of tissues supplied by the damaged capillaries, departures proportional to the change in permeability. If the capillary changes come on gradually, are not too intense in their development and are of sufficient duration, it is reasonable to believe that the resulting inadequate nutrition of tissue would result in connective tissue growth and replacement, and in various types and stages of tissue degeneration. This, of course, is not a new idea. It was expressed in 1872 by Gull and Sutton,[10] who believed that a general morbid state, which they

6. Heubner: Ach. f. exper. Path. u. Pharmakol. **56**:370, 1907.
7. Wallace and Myers: J. Pharmacol. & Exper. Therap. **6**:601, 1915.
8. Faust: Arch. f. exper. Path. u. Pharmakol. **51**:248, 1904.
9. Wallace and Pellini: Am. J. M. Sc. **152**:325, 1916.
10. Gull and Sutton: Med. Chir. Tr. **55**:273, 1872.

termed arteriocapillary fibrosis, may exist, characterized hy hyalin fibroid formation in the walls of the minute arteries and hyalin granular changes in the capillaries. This morbid state is attended with atrophy of adjacent tissues, and the contracted kidney of chronic Bright's disease is only a part of the process. This view has been recently again expressed and enlarged by Moschowitz.[11]

Now, while it is easy to surmise a causal relationship between capillary injury and tissue degeneration, it must be emphasized that this relationship, as far as human pathology is concerned, is as yet a theory and not a fact. In the first place, the existence of poisons which might be expected to cause the capillary damage is hypothetical. In the second place, as Oertel has stated, there is no proof at present that vascular changes are the forerunners of tissue degenerations, and not part of a damaging process which affects capillaries and tissue independently. In order to leave the realm of theory and enter that of fact, it will be necessary, first of all, to produce by means of a known vascular poison, capillary injury which will be followed by tissue degeneration, and to vary the latter according to the extent and duration of the former. Experimental work along this line has so far not been very successful. Most of it has been carried on with the purpose of producing chronic nephritis. Dickson [12] has produced a chronic diffuse nephritis, with severe glomerular lesions, by means of uranium. In advanced cases, along with other changes, there was a thickening of the capillary walls. He believes, however, that the vascular damage is of slight importance. On the other hand Harvey,[13] using parahydroxy phenylethylamin, induced chronic kidney lesions which he considers to be secondary to vascular changes in the renal artery and its branches.

There is one other aspect of the effects of capillary injury, namely, its relation to high blood pressure. The popular conception at present is that at least one type of high blood pressure, the so-called essential hypertension, has as its basic cause a narrowing or obliteration of capillary fields. As is the case with tissue degeneration, this relationship is a very plausible one, but again, is a theoretical conception. The problem does not appear beyond solution, however, and we are at present engaged on it in the hope of eventually getting some positive results.

EXPERIMENTAL WORK

In the course of our work we have looked for capillary poisons which have a wide spread rather than a localized sphere of action. This separation is not as simple as it appears. It seemed to us,

11. Moschowitz: Arch. Int. Med. **26**:259 (Aug.) 1920.
12. Dickson: Arch. Int. Med. **9**:557 (Oct.) 1912.
13. Harvey: J. Path. & Bacteriol. **16**:95, 1911.

however, that a poison which has a rather general effect on capillaries should bring about some measurable change in metabolism, for a lessened capillary permeability ought to lead to a decrease in cell nutriment, and, included with this, a decrease in oxygen. This latter state could readily induce a condition of suboxidation. The ordinary metabolism experiment throws no definite light on this question. There is an increase in nitrogen elimination and other changes, which admit of various interpretations. It seemed, however, that one distinctive type of metabolic derangement might occur, namely, acidosis, and accordingly we have carried out a series of experiments using a number of capillary poisons, and determining their effects on the alkali reserve of the blood. Our results have been definite enough to make it seem desirable to report them in some detail.

The experiments were performed on adult dogs in a good state of nutrition, which were picked indiscriminately from the available laboratory animals. The drug used was given by subcutaneous, intramuscular or intravenous injection. No restriction in diet was made, although in the longer experiments the animals refused food as time went on. Blood to be tested was withdrawn from the external jugular vein once a day or oftener. The blood was received directly without exposure to air, into a tube containing potassium oxalate and mineral oil. It was immediately centrifuged and the serum analyzed for alkali reserve by the Van Slyke method.[14]

We feel it unnecessary to quote all our experiments and are limiting our protocols in general to one typical experiment for each poison tested.

PROTOCOLS OF EXPERIMENTS

Uranium.—Dog, weight, 7.2 kilos; uranium nitrate, 0.021 gm., injected subcutaneously October 5. Alkali reserve before injection 57.7 volume, per cent. carbon dioxid. After injection, October 6, 53.8 per cent.; October 7, 36.8 per cent.; October 8, 29.5 per cent.; October 9, 25.3 per cent.; October 11, 31.5 per cent.; October 12, 23.3 per cent.; October 13, exitus.

The twenty-four hour urine output rose from 330 c. c. on October 6 to 1,084 c. c. October 10. It then fell and was 115 c. c. October 12.

Cantharidin.—Dog, weight 12 kg., cantharidin, dissolved in weak sodium hydrate solution, injected intravenously as follows: November 23, 5 mg.; November, 24, 7.5 mg.; November 25, 26, 27, 10 mg. Alkali reserve, before injection 58 per cent.; after injection, November 24, 58.2 per cent.; November 25, 58.4 per cent.; November 26, 10 a.m., 40.9 per cent., 4:30 p. m., 36.2 per cent.; November 27, 42.5 per cent.; November 28, 30.9 per cent. Animal killed November 28. There was no anuria during the experiment.

Diptheria Toxin.—Dog, weight, 12.1 kg., diptheria toxin m. l. d. 1/500 c. c., (obtained from Dr. W. H. Park), 1.4 c.c. injected intramuscularly at 4:30 p. m. November 30. Alkali reserve before injection, 55.8 per cent. After injection, December 1, 9:30 a. m., 30.3 per cent.; 11:40 a. m., 18.1 per cent. Exitus, December 1.

14. Van Slyke: J. Biol. Chem. **30**:347, 1917.

We have used in these experiments three capillary poisons, two of which, uranium [15] and cantharidin,[16] act especially on the kidney; the third, diptheria toxin,[7] acting equally strongly on the intestinal and liver capillaries, and, in fact, on capillaries generally. The action of uranium and cantharidin is not limited to the kidney, however.

In order to determine to what extent the renal action was concerned in the acidosis, the following experiments were done. In a control animal a double nephrectomy was performed under ether anesthesia and the blood was analyzed during the four following days. In a second animal, a double nephrectomy was performed, and on the following day uranium was injected. We are indebted to Dr. W. H. Barber for the operative procedures. The results were as follows:

Nephrectomy.—Dog, weight, 15.8 kg., double nephrectomy November 10. Alkali reserve, before operation, 57.7 per cent.; after operation, November 11, 49 per cent.; November 12, 60.2 per cent.; November 13, 61.1 per cent.; November 14, 69 per cent.

Nephrectomy and Uranium.—Dog, weight 11.25 kg., double nephrectomy November 16. November 17, 33 mg. uranium nitrate by subcutaneous injection. Alkali reserve before nephrectomy, 50 per cent.; after nephrectomy, November 17, 52.3 per cent.; after uranium, November 18, 44 per cent.; November 19, 38.7 per cent.; November 20, 10 a. m., 33.1 per cent., 2:30 p. m., 30.7 per cent.

It is obvious from these experiments that removal of both kidneys is without influence on uranium acidosis, and that kidney damage is not an appreciable factor in this acidosis.

Emetin.—Dog, weight, 13.1 kg., emetin hydrochlorid, 1 per cent. solution, injected subcutaneously, 2.5 c. c. daily, October 12, 13 and 14; twice October 15, 3 c. c. twice October 16. Alkali reserve, before injection, 63.6 per cent.; after injection, October 12, 63.3 per cent.; October 13, 63.3 per cent.; October 14, 57.9 per cent.; October 15, 57.9 per cent.; October 16, 63.5 per cent.; October 17, 57.6 per cent. Exitus, October 18.

In another emetin experiment a dog was given 21 c. c. of a 1 per cent. solution during a period of four days. At the end of this time, under morphin and light ether anesthesia, blood was withdrawn from the jugular, portal and an intestinal vein at approximately the same time. The alkali reserve was 54.8 per cent., 54.8 per cent. and 53.9 per cent., respectively.

Podophyllotoxin.—Dog, weight, 11.8 kg., podophyllotoxin, dissolved in weak alkali, injected intramuscularly as follows: October 28, 20 mg.; October 29, 30 mg.; October 30, 20 mg.; November 2, 20 mg.; November 3, 30 mg. Alkali reserve, before injection, 57.8 per cent.; after injection, October 28, 58.6 per cent.; October 29, 57.5 per cent.; October 30, 53.9 per cent.; October 31, 58.6 per cent.; November 1, 55.7 per cent.; November 3, 53.8 per cent.; November 4, 53.9 per cent.; November 5, 44.5 per cent. Exitus, November 5, shortly after last blood examination.

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15. McNider: J. M. Res. **31**:79, 1912.
16. Lyon: J. Path. & Bacteriol. **9**:444, 1904.

Emetin [9] and podophyllotoxin [17] act selectively on the intestinal capillaries, and in the experiments just noted necropsy showed the presence of the characteristic intestinal lesions. There was also congestion of the kidney, but the renal damage was not severe, as the urine showed only faint traces of albumin and no striking diminution in quantity. In the second emetin experiment we had expected to find the alkali reserve in the blood from the intestinal and portal veins lower than in that from the jugular vein. In this we were disappointed and have to conclude that marked damage to the intestinal capillaries fails to bring about an appreciable acidosis.

Arsenic.—Dog, weight, 16.7 kg., arsenious acid given subcutaneously in daily dosage of 30 mg., November 18, 19, 20 and 21; intravenously November 22, 30 mg.; November 23, 30 mg.; November 24, 50 mg.; November 25, 70 mg.; November 26, 70 mg.; November 28, 80 mg. Alkali reserve, before injection, 54 per cent.; after injection, November 19, 54.9 per cent.; November 20, 55.9 per cent.; November 21, 55.7 per cent.; November 22, 55.6 per cent.; November 23, 55.6 per cent.; November 24, 55.6 per cent.; November 25, 57.4 per cent.; November 26, 46.2 per cent.; November 27, 45.3 per cent. Exitus, November 28.

In this experiment, the arsenic acted chiefly on the intestinal tract. There was also well marked congestion of the liver and kidneys, and a beginning fatty change in the liver.[18] The acidosis was not marked, and this we attribute to an absence of wide spread capillary damage. In another arsenic experiment we obtained the following result:

Arsenic.—Dog, weight 13.4 kg., 60 mg. arsenious acid injected intravenously at 11:15 a. m. Alkali reserve, before injection, 50 per cent.; at 2:45 p. m., 30.4 per cent. Exitus, 3:15 p. m.

Hydrazin.—Dog, weight, 10.6 kg., hydrazin sulphate injected subcutaneously 100 mg. daily, November 8, 9 and 10; 200 mg. daily November 11, 12, 13 and 14; 400 mg. November 15. Alkali reserve before injection 53.8 per cent.; after injection, November 9, 51 per cent.; November 10, 53.9 per cent.; November 11, 55.7 per cent.; November 12, 62.6 per cent.; November 13, 67.2 per cent.; November 14, 67.1 per cent.; November 15, 65.3 per cent. Exitus, November 16.

This substance is not classed as a capillary poison. It has a highly selective action on liver tissues, however, producing marked destruction and fatty infiltration of liver cells.[19] In another hydrazin experiment comparable to the second arsenic and the diptheria experiments in regard to time, the following result was obtained:

Dog, weight, 618 kg., 600 mg. hydrazin sulphate injected subcutaneously at 3:45 p.m. November 5. Alkali reserve before injection, 52 per cent.; after injection, 11 a. m., November 6, 72 per cent. Exitus, 1 p. m., November 6.

With this marked damage to the liver, we find, therefore, not an acidosis, but the reverse.

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17. Neuberger: Arch. f. exper. Path. u. Pharmakol. **28**:32, 1890.
18. Boehm: Arch. f. exper. path. u. Pharmakol. **2**:89, 1874.
19. Underhill and Klein: J. Biol. Chem. **4**:165, 1908

As the above described experiments show that neither kidney, intestine or liver injury is responsible for the acidosis we have obtained, we carried out the following transfusion experiment to determine whether the muscle tissue is concerned in the process.

January 25 a dog was given 1.75 c. c. diptheria toxin injected intramuscularly. The alkali reserve at 11 a. m. January 26 was 35 per cent. At 11:30 a. m. the femoral artery and vein of this dog were connected with the femoral artery and vein of a normal dog, the latter, therefore, supplying the circulation to the poisoned leg. The necessary operative procedures were carried out under morphin anesthesia, supplemented with a small quantity of cocain. Hirudin was used to prevent clotting of blood The transfusion was maintained for over an hour. The alkali reserve of the normal dog before the experiment began was 55.8 per cent. The figures obtained after 45 minutes of transfusion were, jugular blood, normal dog, 55.4 per cent.; diptheria toxin dog, 31.5 per cent.; femoral blood from poisoned leg, 42.6 per cent.

Using the bloods taken from these two animals just before the transfusion, we have estimated the hemoglobin and blood cells, and made the ordinary chemical analysis.

	Normal Dog	Diptheria Toxin Dog
Red blood cells	6,100,000	6,800,000
Hemoglobin	85%	80%
White blood cells	12,400	26,200
polymorphonuclears	82%	78%
mononuclears	18%	22%
Nonprotein nitrogen	26.3 mg.	62.5 mg.
Urea	16.1 mg.	38.4 mg.
Creatinin	1.5 mg.	1.7 mg.
Sugar	117.6 mg.	44.0 mg.
Whole blood chlorids	500.0 mg.	500.0 mg.

A comparison of the red blood cell count and hemoglobin shows no difference in the concentration of the blood in the two animals. The diptheria toxin animal shows a leukocytosis and in addition the altered blood chemistry which is to be expected, since the toxin acts on the kidney as well as other capillaries.

An experiment of this sort is naturally open to some criticism from the technical factors involved, but the results show that muscle is one of the tissues involved in the production of acidosis.

We have assumed that a suboxidation due to impaired capillary permeability is the cause of the acidosis from capillary poisons. It seemed to us that this assumption would be strengthened by obtaining acidosis through suboxidation induced by other than capillary poisons. The following experiments bear on this point.

Sodium Nitrite.—Dog, weight, 11.6 kg., received by subcutaneous injection 0.1 gm. sodium nitrite January 10 at hourly intervals from 11:45 a. m. to 3:45 p. m., in all 0.5 gm. Alkali reserve before injections, 51.4 per cent., at 4 p. m. 58 per cent. The blood spectroscopically showed no methemoglobin. On the following day, the animal received 0.2 gm. sodium nitrite, at intervals, from

10:45 a. m. to 12:45 p. m., 0.8 gm. in all. Alkali reserve before injection, 56.1 per cent., at 1:10 p. m. 49 per cent., at 1:50 p. m., 29 per cent. At 1 p. m. blood showed methemoglobin.

It appears from this experiment that a lowering of blood pressure which must have been induced by the nitrite on the first day of the experiment was not productive of acidosis. This appeared only on the second day when the formation of methemoglobin occurred. Methemoglobin, of course, means cellular asphyxia.

Potassium Cyanid.—Dog, weight, 11.3 kg., received 34 mg. potassium cyanid January 12 at 11 a. m.; 22 mg. at 11:30 a. m.; 50 mg. at 12 noon. No characteristic symptoms, except vomiting and a slight ataxia occurred until 12:25 p. m., when marked dyspnea and muscle twitchings appeared. Alkali reserve before injections, 53.8 per cent.; after injections, 12 noon, 27.4 per cent.; 12:25 p. m., 12.2 per cent. Exitus during night.

Potassium cyanid has been studied quite extensively from the standpoint of its effect on metabolism.[20] It acts in some unexplained way on tissues, preventing their using available oxygen. It may be noted in this experiment that the acidosis was very definite before any convulsive movements had set in.

We have one other experiment to report. In most of our experiments, as poisoning progressed, there developed a condition of muscular weakness, prostration, narcosis and lessening of the respiratory function. We have reproduced this condition by administering large quantities of morphin. The results are as follows.

Morphin.—Dog, weight 10.3 kg, normal respiration, 20 per minute. December 1, a total of 190 mg. morphin sulphate given by subcutaneous injection at half hour intervals from 10:45 a. m. to 5:10 p. m. The respiration fell to 11 per minute, slightly labored, with moderate narcosis. Alkali reserve before morphin, 64 per cent.; after morphin, at 4:20 p. m., 61.5 per cent. On the following day, morphine was again given, at frequent intervals, from 9:55 a. m. to 3 p. m. In all 2 gm. morphin were injected. At 3:30 p. m. respiration was 10 per minute and shallow, moderate narcosis, animal being unable to stand. At this time the alkali was 64 per cent. Death occurred during the night.

The administration of large amounts of morphin, therefore, with the production of narcosis and respiratory depression, does not cause acidosis. Gauss [21] has recently shown that an actual increase in alkali reserve may occur.

DISCUSSION

In looking over these experiments we find that those poisons which produce a wide spread capillary damage, namely uranium, cantharidin and diphtheria toxin, cause a definite acidosis. The first two of these

20. Richards and Wallace: J. Biol. Chem. **4**:179, 1908.
21. Guass: J. Pharmacol. & Exper. Therap. **16**:475, 1921.

act most strongly on the kidney; but the fact that uranium is equally effective in causing acidosis in nephrectomized animals speaks against renal damage being an essential factor.

Emetin and podophyllotoxin produce very destructive effects along the intestinal tract, and yet neither causes an appreciable acidosis. Again, hydrazin is a powerful liver poison, but its administration in fatal dose is not followed by acidosis.

The transfusion experiment described, in which a diminished alkali reserve is seen in venous blood from a diptheria toxin poisoned extremity, receiving normal arterial blood, offers a clue to the place of origin of the acidosis, and we believe the abnormal metabolism, of which acidosis is one of the evidences, occurs chiefly in muscle tissue.

The explanation of the abnormal metabolism lies, we believe, in a diminished permeability of the damaged capillary wall, the diminution in the oxygen reaching the tissue cell resulting in a state of suboxidation. This belief is strengthened by the experiments with sodium nitrite and potassium cyanid, which show that a failure of the blood to give up oxygen, due to the formation of methemoglobin, or of the tissue to utilize available oxygen, will also cause acidosis.

Finally, in application of our experimental facts, we believe that many cases of clinical acidosis may be explained by capillary injury. An acidosis, for example, may occur in many, if not all of the acute infectious diseases. Thus it has been observed in pneumonia,[22] in diptheria,[23] in scarlet fever [24] and in influenza.[25] While little is known concerning the toxins in most of these infections, in one at least, diptheria, the toxin is known and is the poison which, in our experiments, produced the most striking degree of acidosis obtained.

Among other clinical cases which were accompanied by acidosis we find nephritis,[26] and cardiac disease.[27] These conditions are considered by many to be part of a general vascular disease, the arteriocapillary fibrosis of Gull and Sutton, and looking at them from this standpoint, a relationship between the acidosis and capillary injury can easily be assumed.

SUMMARY

1. Those poisons which have a wide spread action on capillaries, produce a marked degree of acidosis. Among these are diptheria toxin, uranium and cantharidin.

22. Palmer: J. Exper. M. **26**:495, 1917.
23. Peters: Brit. M. J. **1**:10, 1918.
24. Thomas: Ibid. **1**:274, 1919.
25. Hachen and Isaacs: J. A. M. A. **75**:1624 (Dec. 11) 1920.
26. Peabody: Arch. Int. Med. **16**:955 (Dec.) 1915.
27. Peabody: Ibid. **14**:23 (July) 1914.

2. Renal injury is not an essential factor in the acidosis, since double nephrectomy fails to produce acidosis, and this condition can be brought about in nephrectomized animals.

3. Those poisons which act selectively on the intestinal capillaries fail to produce acidosis, or if so, produce it to a minor degree.

4. Marked injury to liver tissue does not cause acidosis.

5. Evidence is submitted which points to muscle tissue as being one of the seats of acid formation.

6. The assumption is made that the cause of the acidosis is a condition of suboxidation in the tissues, and experiments are reported showing that suboxidation produced by other means than capillary poisoning also causes acidosis.

7. Capillary poisoning is suggested as an explanation of acidosis occurring in acute infectious diseases and some other clinical conditions.

LOCAL DESENSITIZATION IN HYPERSENSITIVE INDIVIDUALS AND ITS BEARING ON THE PREVENTION OF HAY-FEVER *

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Cutaneous reactions in hypersensitive individuals are of two quite distinct types. The reactions frequently observed in patients with hay-fever or bronchial asthma and those obtained after sensitization by foreign serum consist essentially of an urticaria-like lesion with a central wheal and a surrounding zone of erythema. Such reactions appear a few minutes after application of the test substance, usually reach their full development in half an hour or less, and fade out completely in one or two hours. The skin, at the site of the test then appears normal. There is no visible evidence of cell destruction. It appears to be essentially a vascular phenomenon with localized edema. Such reactions may often be obtained in hypersensitive individuals with extracts of pollens, animal hair, dandruff or feathers, with foreign serum, with many food proteins and occasionally with bacterial or other proteins.

These immediate urticaria-like reactions have little in common with the local cutaneous reactions produced by tuberculin, typhoidin, luetin and mallein. Here, the reaction does not develop for a number of hours; it is characterized by induration and persistent signs of inflammation, requires many days to fade out completely and clearly involves cell destruction. Zinsser [1] has recently shown that the local tuberculin reaction in the guinea-pig is independent of the development of a state of anaphylaxis, and it is highly probable that the same holds true for the reactions of this type produced by other substances of bacterial origin.

Although it has commonly been assumed that the immediate skin reactions with urticaria-like lesions are manifestations of anaphylaxis, it has not been demonstrated that the mechanism consists of an antigen-antibody reaction. Similar reactions may sometimes be obtained with nonantigenic substances, such as salicylates and quinin, and there are a few substances, notably histamin, morphin and pituitary extract which produce this type of reaction in normal individuals.

In an effort to determine the nature of these urticaria-like skin reactions, we have studied their exhaustibility in eight hypersensitive

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1. Zinsser, H.: Proc. Soc. Exper. Biol. & Med. **18**:123, 1921.

individuals, six of whom had hay-fever or bronchial asthma, and two of whom were hypersensitive to horse serum following the intravenous administration of antipneumococcus Type I serum.

TECHNIC

Both the cutaneous and intracutaneous methods of eliciting the skin reaction have been employed. The former was done by the familiar cut method, using a small, sharp scalpel to make a superficial incision about 2 mm. long through the outer layers of the skin. To the cut is applied a drop of tenth normal sodium hydroxid and in this drop of alkali, a small amount of the test substance in powder form is rubbed into solution or an even suspension by means of a

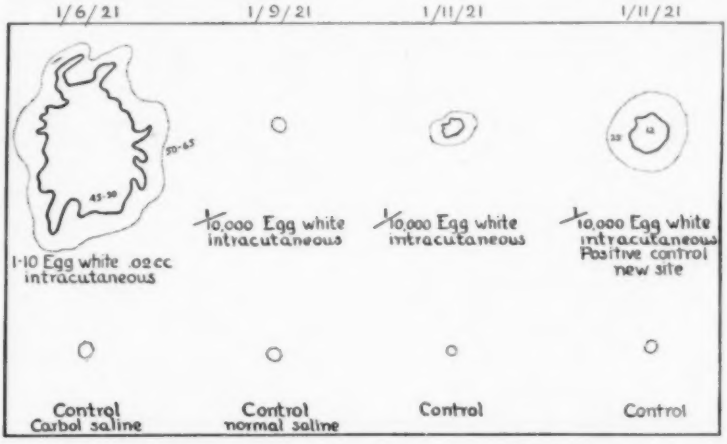

Fig. 1.—A. McL. No. 48423. Male. Age 6. Bronchial asthma and hypersensitiveness to egg. In this and the following figures the inner solid line figure represents the outline of the wheal and the outer dotted line represents the surrounding zone of erythema. The figures show the actual size in millimeters of the wheal and zone of erythema. Above the drawings, the date when each test was done is shown. Positive controls on new sites were done Jan. 9, and Jan. 11, 1921. They were of the same size and appearance. Only the latter is shown. The test on Jan. 6, 1921 with a 1 : 10 dilution of egg white was followed by a general reaction so that in the subsequent tests, a weaker solution was used. It is seen that after an interval of three days, there was no reaction at the site of the initial test and that after five days, the reactivity had only partially returned.

sterile tooth pick. It was found that repeated applications of a drop of tenth normal sodium hydroxid to the same site frequently caused a small area of inflammation so that normal salt solution was substituted for the alkali. For the substances used, this gave specific reactions as strong as those obtained with alkali as solvent and did not cause any

irritation of the skin. In the tests with egg white and horse serum, physiologic sodium chlorid solution containing 0.5 per cent. phenol was used as a diluent.

The intracutaneous tests were carried out by the usual technic, consisting of an injection of 0.02 c.c. into the superficial layers of the skin. If properly done, a small injection wheal about 3 mm. in diameter should form when the solution is injected. It was found that the latter method lends itself better to the demonstration of the exhaustion of the skin reaction than the cutaneous technic, although the reactivity may be abolished by either method.

It was found that the exhaustion of reactivity is not readily demonstrable unless the application or injection of the test substance is repeated at short intervals. Usually, we repeated the test as soon

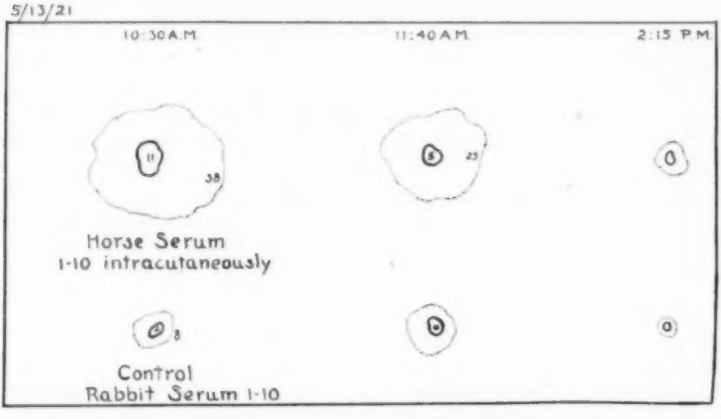

Fig. 2.—B. S. No. 5901. Female. Age 27. Bronchial asthma. Hypersensitiveness to horse dander and horse serum. This patient was spontaneously hypersensitive to horse serum though only to a moderate degree. The local exhaustion of reactivity was accomplished by two intracutaneous reactions with 1:10 dilution of horse serum.

as the preceding reaction had subsided, except when it was necessary to wait until the next day before completing the exhaustion. The intervals in most cases between applications were therefore from one to three hours. Some of the proteins used (almond, pea, oat, wheat) were obtained from a commercial firm, the egg white was prepared by making dilutions of fresh egg white in phenolized physiologic sodium chlorid solution; the ragweed extract was prepared by extracting the pollen with one hundredth normal sodium hydroxid, filtering through paper and a Mandler candle; the horse serum was obtained from the Department of Health of New York City.

RESULTS

The semidiagramatic drawings (Figs. 1 to 8) illustrate eight of the thirty-six observations made on the eight patients. These results indicate that the specific reactivity of the skin may readily be abolished locally by repeatedly applying to the same site the substance to which the individual manifests cutaneous hypersensitiveness. The exhaustion has been accomplished with such biologically different substances as egg white, horse serum, extracts of ragweed and chicken feathers, the proteins of almond, pea, oat and wheat. Moreover, the reactivity is

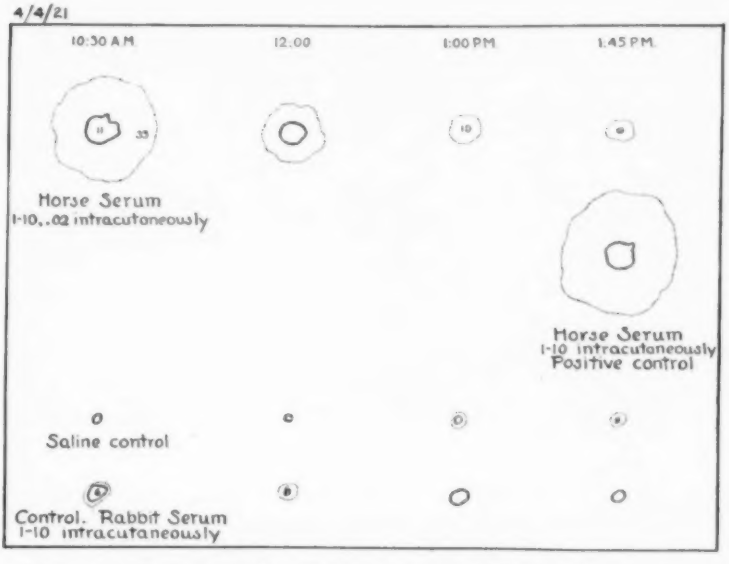

Fig. 3.—G. R. No. 49327. Male. Age 23. Patient had pneumococcus Type I pneumonia, was given 500 c.c. of antipneumococcus Type I serum. Serum disease developed on the seventh day after first serum treatment and persisted till the twelfth day. Cutaneous hypersensitiveness to horse serum developed on the fourteenth day after first serum. The figures represent the local exhaustion of reactivity to horse serum in a patient whose cutaneous hypersensitiveness was artificially produced. On admission to the hospital, the intracutaneous reaction with a 1:10 dilution of horse serum was negative.

more quickly abolished with concentrated than dilute solutions. Figure 1 shows that with a 1:10 dilution of egg white, a single intracutaneous test on a child 6 years old with bronchial asthma and hypersensitiveness to egg, completely abolished the skin reactivity at the site of the reaction. In Figure 2, the local exhaustion of reactivity in a patient spontaneously hypersensitive to horse serum is shown, and in Figure 3,

the same thing is shown for a patient artificially sensitized by serum treatment. In both these patients, the reactivity was quickly abolished.

In other trials, when substances presumably less antigenic were being tested or when weaker solutions were used, and the cutaneous technic was employed, from four to eight repetitions of the test were required to complete the exhaustion. In Figure 4, the exhaustion by means of the cutaneous technic is shown. In this instance, the reactivity persisted until the test had been repeated five times. The duration of the exhaustion has likewise been found to be dependent to some extent on the concentration of the protein solution and the method employed for producing the reaction. Thus, in Figure 1, it is shown

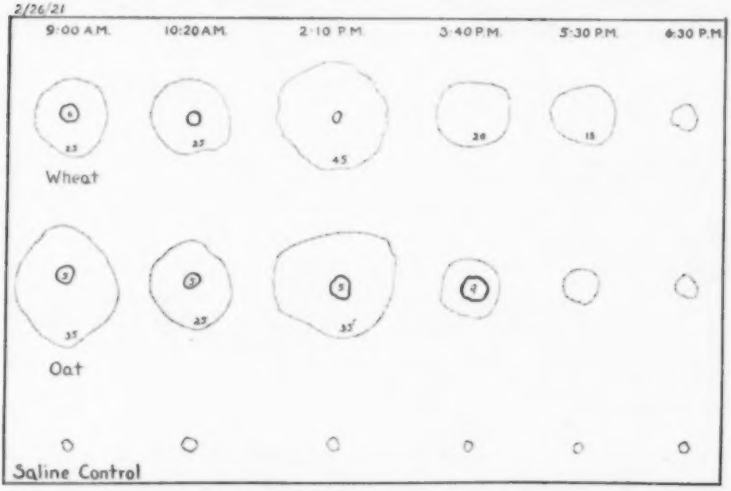

Fig. 4.—B. Y. No. 49217. Male. Age 33. Bronchial asthma, hypersensitiveness to wheat, oat, rye, barley, rice. The local exhaustion of reactivity to wheat and oat is here shown to have been accomplished by the cutaneous technic after five applications.

that the reactivity of the child's skin at the site of the test was completely abolished for three days and partially abolished for five days. In other instances, with less concentrated solutions and substances whose antigenic properties are weaker, the exhaustion did not persist for more than twenty-four hours.

The extent of the area in which the reactivity is abolished is strictly limited to the site of the reaction. The area actually occupied by the wheal becomes completely exhausted, the area of the erythema partially so, and beyond this, the skin reacts as strongly as at a fresh site.

In order to determine the specificity of the exhaustion, we have made observations on three patients who gave clean-cut positive reactions to more than one substance. After simultaneously exhausting the reactivity of the skin at one site to one protein and at another site to a different protein, each protein was tested on the site exhausted by the other protein. Although the number of patients on whom it has been possible to study in this way the specificity of the exhaustion is too small to justify conclusions, the observations made thus far suggest that there is a strict specificity for substances biologically unrelated and something similar to group reactions for substances closely related biologically. Figure 5 shows the reactions of a patient

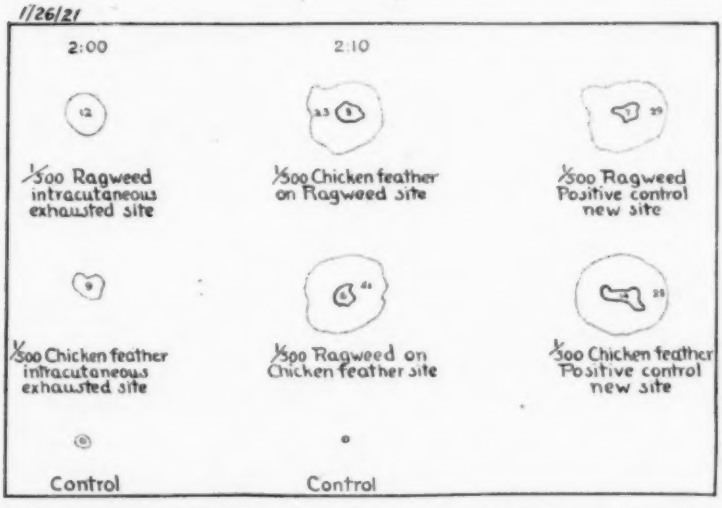

Fig. 5.—D. H. No. 48838. Male. Age 52. Bronchial asthma and hay fever. Hypersensitiveness to ragweed and chicken feather. At the left are shown the reactions to ragweed and chicken feather after repeated intracutaneous tests at these sites had almost completely abolished the reactivity. Chicken feather was then tested on the exhausted ragweed site and ragweed on the exhausted chicken feather site. At the same time, each was injected at a fresh site. It is seen that the exhaustion is specific for both ragweed and chicken feather.

who manifested cutaneous hypersensitiveness to ragweed and chicken feather. It is seen that the exhausted ragweed site reacted as strongly to chicken feather as a fresh site and vice versa. Figure 6 in the same way illustrates the specificity of the exhaustion for the proteins of almond and pea. There is clearly no close biologic relation between ragweed and chicken feather nor between almond and pea. Figure 7, however, records the reactions of a patient hypersensitive to oat and wheat. It is seen here that the result suggests a group reaction. The

site which had been exhausted with wheat shows also a partial exhaustion of the reactivity to oat, for the exhausted wheat site reacted less strongly to oat than a fresh site.

As a control series of observations, we have attempted in six patients to abolish the nonspecific cutaneous reactions to histamin. It is well known that histamin, either intracutaneously or by application to a small cut or scarification of the skin, produces an urticarial lesion quite similar in appearance to the reactions of individuals hypersensitive to pollen, animal dandruff, or feather extracts. Sollman [2] has studied the exhaustibility of the histamin skin reaction. With the scarification method, he found it inexhaustible. With the cut method and by intra-

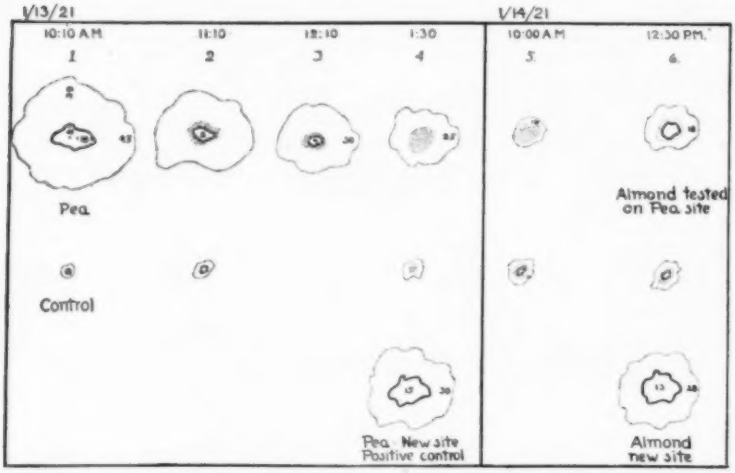

Fig. 6.—M. K. Female. No. 47992. Age 24. Bronchial asthma, urticaria, angioneurotic oedema. Hypersensitiveness to pea, buckwheat, cauliflower, lentil, almond. The first five figures in the upper row represent the successive stages of exhaustion of a skin area with pea protein by the cutaneous method. The sixth figure in the upper row represents the reaction to almond protein on the area in which reactivity to pea protein had been abolished. It is seen that this reaction is only a little less intense than the reaction produced by almond at a fresh site, shown in the lower right hand corner. The control reactions are shown in the second row. The reaction to pea at a fresh site, serving as a positive control, is also shown in the third row.

cutaneous injections of a 0.1 per cent. solution, we have found that it is not only inexhaustible, but that the size and intensity of the reaction progressively increase with each subsequent application. Furthermore, exhaustion of the reactivity of a skin area with a specific antigen does not render this area refractory to histamin. In Figure 8 it is seen

2. Sollmann, T.: J. Pharmacol. & Exper. Ther. **10**:147, 1917.

that the site which had been exhausted for egg white gave a reaction to histamin which equals in intensity the histamin reaction at a fresh site.

The nonspecific cutaneous reaction of pituitary extract has likewise been found to be inexhaustible. With morphin sulphate, using a 3 per cent. solution, the reaction, after four or five applications to the same site, has sometimes been inexhaustible, while at other times there was a partial loss of reactivity for a few hours.

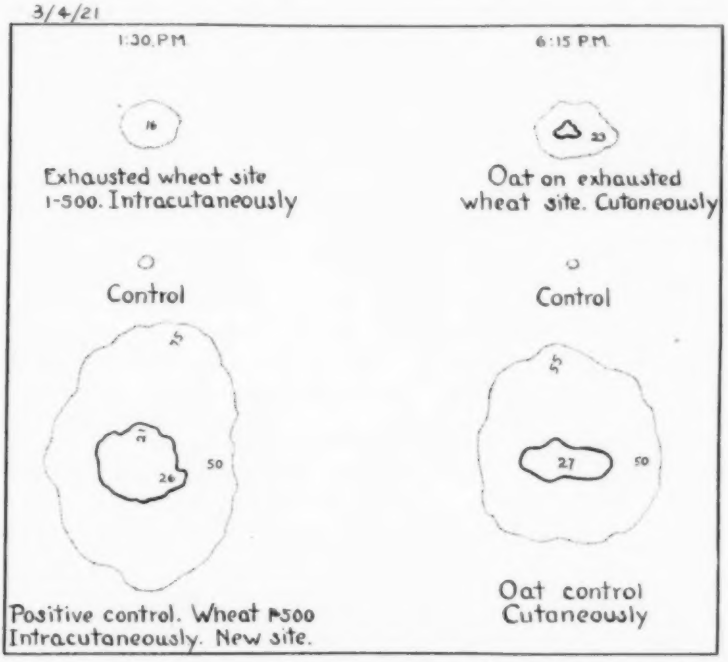

Fig. 7.—B. Y. No. 49217. Male. Age 33. Bronchial asthma, hypersensitiveness to wheat, oat, rye, barley, rice. Above at the left is shown the reaction by the intracutaneous technic of a 1:500 dilution of wheat after the reactivity had been almost completely abolished by eight previous tests at the same site during the preceding forty-eight hours. Below this is shown the control reaction, using only the solvent, and below this, the reaction at a fresh site to the same solution of wheat protein. The figures to the right show, above, the reaction to oat at the exhausted wheat site and, below, the reaction to oat at a fresh site. It is seen that the exhaustion by wheat has effected a partial exhaustion for oat.

DISCUSSION

The observations which we have described indicate that if the protein to which a patient manifests cutaneous hypersensitiveness is

repeatedly applied, either cutaneously or intracutaneously at short intervals to the same area of skin, the reactivity of the skin may be abolished locally. Furthermore, this exhaustion appears to be specific, for, if a patient gives positive skin reactions to two substances, biologically unrelated, the reactivity of an area of skin may be abolished for one substance without loss of reactivity for the other. Repeated efforts to abolish locally the reactivity of the skin to histamin have without

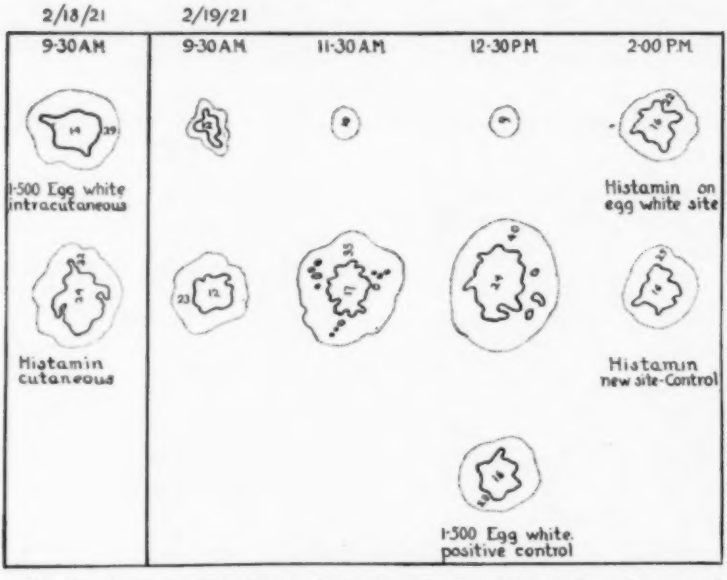

Fig. 8.—A. McL. No. 48423. Male. Age 6. Bronchial asthma, hypersensitiveness to egg. The first four figures in the upper row represent the exhaustion of a skin area by the intracutaneous injection of a 1:500 dilution of egg white. It is seen that after the injection had been made twice, the reactivity was abolished for egg white. The figure furthest to the right in the upper row represents the reaction to histamin on the exhausted egg white site. It is seen that the histamin reaction is just as strong on this area as on a fresh site. The second row of figures illustrates typically the effect of applying histamin repeatedly to the same site. It is seen that the intensity of the reaction increases with each repetition after the first.

exception resulted not only in failure to accomplish the exhaustion, but in a demonstration that the nonspecific histamin reaction progressively increases in intensity with each subsequent application. To us it seems significant that the nonantigenic substance histamin produces a reaction which is inexhaustible, while the reactions produced by the antigenic substances which we have employed are readily exhaustible. Perhaps, the further observation that those substances

which are highly antigenic, such as egg albumin and horse serum, effect the exhaustion more promptly than less antigenic substances, such as pollen and feather extracts, is also significant. While the analogy between our results and the phenomena of antigen-antibody reactions is striking, we do not feel that one is justified as yet in interpreting the analogy as necessarily indicative of a similar mechanism. They do show, however, that the immediate urticaria-like cutaneous reactions of hypersensitive individuals behave much as one would expect them to behave if it were known that the mechanism consisted of an antigen-antibody reaction. The possibility naturally suggests itself that the local exhaustion of reactivity depends on a union of the test substance with something within the cells, and that as a result of this union, the constituent of the cells participating in the reaction is used up or becomes unavailable; that subsequently this intracellular reacting substance is released from the union or that it is reformed, enabling the cells to react again. At any rate, the phenomenon is certainly a local process and not a general one.

Owing to the long period of time required for such allergic skin reactions as that produced by tuberculin to develop and subside, it is not possible to test in the same way as we have done the local exhaustibility of cutaneous allergy of this type. Nor have we yet had an opportunity to try the exhaustibility of the immediate urticaria-like reactions occasionally produced by such nonantigenic substances as quinin and salicylates.

That exposure of tissue cells to contact with an antigenic substance may produce a local alteration of reactivity toward that antigen has recently been demonstrated by Besredka [3] in his studies on local immunity. He has shown that administration of a formed antigen by mouth produces a local immunity in the gastro-intestinal tract apparently residing in the cells of the mucosa. An important factor in this immunity appears to be the decreased permeability of the mucosa for the antigen. Results of the same kind were obtained by Besredka in experiments in which the antigen was introduced intratracheally. In a similar way, our results indicate that in individuals with cutaneous hypersensitiveness, cellular reactivity may be altered locally by repeatedly bringing the antigen in contact with those cells.

With Besredka's results and our own in mind, we have commenced applying this principle therapeutically in hay-fever and allergic rhinitis from such substances as Florentine orris (a frequent constituent of face powders) and horse dander. From what we have observed in the treatment of these patients, it is clear that the local application of pollen, horse dander, or orris extracts brings about an alteration of

3. Besredka, A.: Ann. de l'Inst. Pasteur, **33**:301, 557, 882, 1919; ibid, **34**:361, 1920.

the reactivity of the nasal mucosa toward these substances with the result that the local tolerance is greatly increased. In some of our patients, after from four to six weeks of daily local application of the substance to which the individual is hypersensitive, the nasal mucosa has tolerated, without reaction, more than a thousand times the amount which at the outset caused marked symptoms. We intend to report later the therapeutic results in a group of patients treated in this way.

SUMMARY

1. Observations are reported which indicate that in individuals manifesting cutaneous hypersensitiveness, the reactivity of the skin may be abolished locally by repeatedly applying to the same skin area the substance to which the individual is hypersensitive.

2. The reactivity of the skin at the exhausted site may not return for three days, or perhaps longer.

3. The exhaustion appears to be specific.

4. The extent of the area of the exhaustion is strictly limited to the site of the reaction.

5. The nonspecific cutaneous reaction produced by the nonantigenic substance histamin is not only inexhaustible but progressively increases with each repetition of the application to the same site.

6. The possibility that the results reported indicate a genuine local desensitization is discussed.

7. The bearing of the results on the treatment of hay-fever and other forms of allergic rhinitis is discussed.

PRIMARY CARCINOMA OF THE LUNGS*

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INTRODUCTION

The relative rarity of primary carcinoma of the lungs and bronchi, the difficulty of making a clinical diagnosis and the comparative inaccessibility in regard to surgical procedures, have tended to limit the practical interest in these tumors. In spite of these limitations, there is a very extensive literature on the subject which suggests, at least, a wide scientific interest in this group of neoplasms.

This paper is based on the study of five cases of primary carcinoma of the lungs. The object will be to give a brief résumé of the pathology of carcinoma of the lungs, with some emphasis on the problem of histogenesis and on the possible etiologic importance of acute and chronic irritation.

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GENERAL CONSIDERATIONS

Historical.—The earliest published record of a pulmonary carcinoma is Morgagni's [1] description of a necropsy in which the only finding was an "ulcus cancrosum" of the right lung. The second noteworthy contribution to this subject was Bayle's [2] clinical and pathologic study of three cases which he described under the name of "phthisie cancereuse." He described the co-existence of cancer and tuberculosis, but did not give a clear idea of the difference between the two conditions. He believed that tuberculosis was the result of an acid and cancer of an alkali. He correctly stated that pulmonary neoplasms may exist without symptoms for a relatively long time. The phrase "phthisie cancereuse" was the subject of a prolonged discussion, and led to great confusion between cancer and tuberculosis of the lungs. Laennec [3] described "encephaloid" tumors of the lungs, and many authors of this period used the terms "fungus hematodes" and "fungus of the lungs" to describe malignant pulmonary tumors.

The great advance in the study of lung tumors came with the development of cellular pathology under the influence of Virchow. Since this time the question of the histogenesis of these tumors has absorbed the interest of many investigators. Three sites of origin for pulmonary carcinoma have usually been given; (1) the bronchial mucous membrane; (2) the bronchial mucous glands, and (3) the alveolar epithelium. The fact that there have been great differences of opinion concerning the characteristics of these three types of tumor, indicates the difficulties of coming to a definite conclusion in an individual case. Among the earlier histologic studies is that of Langhans [4] in which he described a case generally accepted as arising from the bronchial mucous glands. The subsequent development of the subject may be outlined briefly by noting a few of the numerous attempts to collect the reported cases. Reinhard [5] collected twenty-seven cases. Wolf [6] reported thirty-one cases from the Dresden Pathological Institute. A year later Paessler [7] was able to find seventy cases in the

1. Morgagni, J. B.: De sedibus et causis morborum per Anatomen indigatis (quoted by Wolff, J.[19]) 1708.
2. Bayle, G. L.: Recherches sur la phthisie pulmonaire, Paris, 1810. (Quoted by Wolff, J.[19])
3. Läennec, R. T. H.: De l'auscultation médiate, on traité du diagnostic des maladies des poumons et due coeur, Paris, 1818. (Quoted by Wolff, J.[19])
4. Langhans, T.: Primärer Krebs der Trachea und Bronchien, Virchows Arch. f. path. Anat. **53**:470, 1871.
5. Reinhard, W.: Der Primäre Lungenkrebs, Arch. f. Heilk. **19**:369, 1878. (Quoted by Paessler.[7])
6. Wolf, K.: Der Primäre Lungenkrebs, Fortschr. d. med. **13**:725, 765, 1895.
7. Paessler, H.: Ueber das Primäre Carcinom der Lunge, Virchows Arch. f. path. Anat. **145**:191, 1896.

literature and added four new cases. Sehrt [8] reviewed 177 published cases. Adler [9] collected a total of 374 cases and since that time Scott and Forman [10] (1916) have found reports of 120 additional cases.

It may be of interest to review briefly some of the data which these reports have brought together.

Incidence.—Composite statistics show that primary malignant tumors of the lungs occur in about 1 per cent. of all carcinomas and in about 0.36 per cent. of all necropsies. The older statistics give a smaller percentage. Reinhard [5] reported 8,716 necropsies at the Dresden City Hospital in which there were five primary lung tumors in a total of 545 cases of carcinoma. Fuchs [11] (Munich) found eight cases of primary lung cancer in 12,307 necropsies. The percentages quoted above are based on the following reports. Among 16,578 cancer necropsies compiled by Adler,[9] there are 168 primary lung tumors. Weller [12] quotes statistics showing forty cases in a total of 11,903 necropsies. There is, however, a growing opinion that primary malignant tumors of the lungs are more common than these statistics indicate. In spite of the prevalence of this opinion, these figures are corroborated in a comparatively recent paper by Scott and Forman,[10] who report three primary bronchial tumors in a series of 302 deaths from malignant disease.

Age.—The following table from Adler [9] gives the age incidence in 356 cases.

TABLE 1.—AGE INCIDENCE OF LUNG CANCER

Age	No. Cases
1-10	0
10-20	6
20-30	10
30-40	30
40-50	78
50-60	113
60-70	94
70-80	23
80-90	2
Age not stated	18
Total	374

8. Sehrt, E.: Beiträge zur Kenntnis des primären lungen Carcinom, Inaug. Diss., Leipzig, 1904.

9. Adler, I.: Primary Malignant Growths of the Lungs and Bronchi, New York, 1912.

10. Scott, E., and Forman, J.: Primary Carcinoma of the Lungs, Med. Rec. **90**:452, 1916.

11. Fuchs, E.: Beiträge zur Kenntnis der geschwulstbildungens in der Lunge, Inaug. Diss., München, 1886. (Quoted by Watsuji.[11])

12. Weller, C. V.: Primary Carcinoma of the Larger Bronchi, Arch. Int. Med. **11**:314 (Feb.) 1913.

Clinical Characteristics.—Lung tumors are only rarely diagnosed clinically. The difficulties of diagnosis are obvious, and the reason for failure in a large percentage of the cases is evident when we consider that the symptoms on which a diagnosis might be made are the result of extensive damage to the pulmonary parenchyma or bronchial obstruction, producing interference with the respiratory function. Furthermore, it is clear that, generally speaking, such signs and symptoms do not serve to differentiate pulmonary tumors from many other intrathoracic conditions.

With the purpose of studying the clinical characteristics of primary bronchial carcinoma, Weller has collected ninety cases in which the diagnosis was based on microscopic examination at necropsy and in which there was good evidence of bronchial origin. He divides these tumors into three clinical groups: (1) small tumors producing no clinical symptoms; (2) tumors in which the dominant symptoms are produced by cerebral or other metastases, and (3) those in which the patient is first seen in a moribund condition; to these groups may be added, (4) those showing symptoms and signs of a more or less extensive pulmonary involvement with or without evidence of metastases.

In the series of ninety cases collected by Weller,[12] a clinical diagnosis was made in ten instances. He has outlined the chief symptoms as follows: (1) cough, (2) dyspnea, usually progressive in character; (3) hemoptysis, varying from blood streaks to bright red blood (the "black currant jelly" or "raspberry jelly" sputum long considered characteristic of these tumors is rarely mentioned); (4) pain, usually referred to chest or shoulder and arm on the affected side, and (5) symptoms due to pressure on important mediastinal structures.

Weller emphasizes the diagnostic importance of the absence of fever and night sweats, of bronchoscopic and radiographic examinations, and of histologic examinations of excised lymph nodes.

Metastases.—Widespread metastases are relatively common findings in primary lung tumors. An analysis of 327 cases in which the distribution is definitely stated (Adler,[9] Lambert [13]) shows thirty-three cases in which there were absolutely no metastases and sixty-three cases in which metastases were confined to the thoracic cavity. The remaining cases showed a high percentage of generalized metastases. On this basis carcinoma of the lungs may roughly be divided into three classes: (1) those showing no metastases; (2) those in which secondary foci were limited to the thorax, and (3) those showing generalized metastases. The possible pathways through which extension may take place are obviously the lymphatics, the blood vessels and the air spaces.

13. Lambert, R. A.: Personal communication.

In some cases of generalized carcinomatosis, almost every organ and part of the body may be involved; but the organs most commonly the seat of secondary tumors are, in approximate order of frequency, the regional lymph nodes, liver, kidneys, lungs, pericardium, abdominal lymph nodes, pleura, brain, suprarenals, bones, cervical lymph nodes and heart.

Anatomy and Embryology.—Before discussing the classification of these tumors, a brief review of the developmental stages, the normal anatomy, and the lymphatic drainage of the lungs is important.

The embryology may be recalled by quoting briefly from Flint.[14]

> In the organogenesis of the lungs, we have the stem and main bronchi consisting of simple tubes lined by a double layer of epithelium, the inner of which is columnar, while the outer is composed of small polygonal cells. . . . Later, the mucosa is thrown into a series of longitudinal folds, while from the cuticular border of the inner row of cells, cilia develop. From the bottom of the crypt-like invaginations formed by the longitudinal folds of epithelium, glands begin to grow into the submucosa, which sometimes pass between the developing muscle bundles into the deeper layers of this coat. As this process takes place there is a differentiation of some of the epithelium into goblet cells, a process, which one also observes in the glands, giving rise to a series of submucous glands with partly serous and partly mucous cells. . . . As we follow the bronchi peripheralward, they become simpler and essentially younger in structure and yet develop their adult characteristics in precisely the same way. The epithelium soon becomes single layered and of a columnar type as the periphery is reached. Finally it takes on a distinct, flat, cubical form. . . . And finally, after birth there is a dilatation of the lobules and further flattening occurs.

The mucous membrane of the trachea and the larger bronchi is composed of three layers, an outer cylindrical layer of ciliated and goblet cells, a middle layer of spindle shaped cells, and an inner layer of wedge shaped, formative cells which rests on the basement membrane. The trachea and the larger bronchi are provided with numerous small mucous glands which are situated within the submucosa, within the fibrous layer and between the cartilaginous rings. Within the lungs the cartilaginous rings occur in bronchioles measuring as small as 1 mm. in diameter. Mucous glands are found throughout the greater part of the bronchial tree. They are most numerous in the larger bronchi and they are rarely, if ever, found in bronchioles measuring less than 1 mm. in diameter. The mucous membrane, even in the smaller bronchioles, retains its ciliated columnar character, but consists of a single layer of cells. Finally, the bronchioles lose their cylindrical character and there is a transition from the columnar epithelium to a nonciliated layer of cells. At the termination of the lobular bronchioles and within the alveoli, the epithelium is of the flat pavement variety.

14. Flint, J. M.: The Development of the Lungs, Am. J. Anat. **6**:1, 1906.

The lymphatics of the lung may be divided into a superficial and a deep set (Miller[15]). The former comprise the pleural lymphatics; the latter comprise those situated in the peribronchial and perivascular areas, as well as those found in the interlobular connective tissue septa.

The bronchial, the arterial and the venous lymphatics anastamose freely but form separate plexuses. The larger bronchi have two sets of lymphatics which enclose the cartilages but are connected by numerous intercartilaginous anastomosing vessels. These lymphatics become smaller and less numerous, finally terminating at the distal end of the lobular bronchioles. There are no lymphatics distal to the lobular bronchioles, that is, in the walls of the atria or alveoli. The periarterial plexus also becomes gradually smaller, and the smaller arterioles are frequently accompanied by only a single lymphatic. The common anastamoses between the bronchial and arterial lymphatics are found at the points of division of the bronchi and at the distal ends of the lobular bronchioles. The pulmonary veins arise from the pleura, the alveolar walls, the distal ends of the lobular bronchioles, and from the points of division of the bronchi; lymphatic channels arise with the veins from all of these locations except the alveolar walls, where there are no lymphatics. The complexity and size of these lymphatics increase with the size of the veins. The lymphatics accompanying the veins from the pleura and from the bronchi anastamose, respectively, with the pleural and bronchial lymphatic plexuses. The most constant valves are situated in the interlobular septa, at the junction of the venous and pleural lymphatics. These valves point toward the pleura. There are no other anastamoses between the pleural and the pulmonary lymphatics. The pleural lymphatics form a dense complicated plexus with numerous valves. The anastamoses are very numerous and the valves offer no resistance to the flow in any direction. The normal flow is over the surface of the lung toward the hilum. The normal flow of the pulmonary lymphatics is likewise toward the hilum. Throughout the lungs, the lymphatics generally have no valves; however, they are sometimes present in the large perivascular channels.

CLASSIFICATION

Primary carcinoma of the lungs and bronchi may be classified according to (1) gross anatomy, (2) histology and (3) histogenesis.

Classification According to Gross Anatomy.—The gross anatomic appearance of lung tumors is very variable and there are no well defined gross types. A nodular form, an infiltrating form, and a miliary carcinosis have been described, and these descriptive terms are frequently used in classification, although they are obviously appli-

15. Miller, W. S.: Studies in Tuberculous Infection. III. The Lymphatics and Lymph Flow in the Human Lung, Am. Rev. Tuberc. **3**:193, 1919.

cable rather to stages in the growth of a tumor than to distinct types of tumor. The nodular form includes rare cases of a single nodule or a few small nodules in the pulmonary parenchyma, or localized papillary tumors arising in the walls of tuberculous or bronchiectatic cavities and are only discovered incidentally at necropsy. The infiltrating form is the usual finding, as the majority of cases are seen in an advanced stage when there is extensive invasion or infiltration of the lung. In these tumors the most significant gross finding is that the tumor is confined to, or is much more extensive in, one lung, while secondary tumors are frequently distributed widely throughout both lungs. In advanced stages of the primary tumors, the distribution of the cancerous invasion within the lung is quite uniform. The bronchi and blood vessels are encircled by bands of tumor, which become more and more conspicious as the hilum is approached. These peribronchial tumor masses may compress the larger bronchi with resulting total or partial occlusion leading to atelectasis and bronchiectasis. A large mass of carcinomatous tracheobronchial lymph nodes is frequently found filling the angle between the main bronchi. The hilic nodes on the opposite side are not infrequently involved, but the opposite lung itself is relatively free from tumor nodules. The cases described as a miliary carcinosis are said to resemble miliary tuberculosis, except that the nodules are somewhat larger, more translucent and whiter in color, and are situated only along the course of the lymphatic channels. This finding is apparently indicative of an early widespread lymphatic invasion of the lung.

Classification According to Histologic Anatomy.—In fifty-five cases reviewed by Weller [12] the structural character of the neoplasm was spoken of as alveolar, acinar, or adenomatous in forty-five, medullary in five, scirrhus in three and simplex in two. According to the cell type these cases were described as squamous in twenty-five, cylindrical in eighteen, polymorphous in ten, round or oval in two and gland and cuboidal in one each. Notwithstanding this variety, it is probable that all cases can be placed in three types; (1) cylindrical cell, (2) polymorphous cell and (3) squamous cell.

The largest number of cases are placed in the cylindrical cell group by the majority of writers (Langhans,[4] Wolf,[6] Paessler,[7] Adler,[9] et al). There are great variations in the histologic characteristics of these tumors, and not infrequently several different types of cell are found in the same tumor. Among the types are: cylindrical cells with and without cilia (Horn [16]), cuboidal cells, polymorphous cells, and mucous secreting cells. The predominating cell is, in most cases, of the

16. Horn, O.: Ein Fall von primären Adenocarcinom der lunge mit flimmerndemzylinderepithel, Virchows Arch. f. path. Anat. **189**:414, 1907.

cylindrical or cuboidal type. The polymorphous cell tumors include those cases in which the predominating cell is of an undifferentiated type and cannot be included in the cylindrical or the squamous cell groups. The squamous cell tumors are said by many investigators to be an infrequent type, but Watsuji [17] places 32.2 per cent. in this category. This difference of opinion may be due to a difference in the interpretation of what constitutes a squamous cell. By some writers only those cells are so classed which tend to undergo keratinization. Ernst [18] insists on this qualification and says that the presence of flattened cells alone or even epithelial whorls is not sufficient basis for calling a tumor squamous celled, since other types of cell may undergo such physical modification. From a critical review of the reported cases it is clear that while tumors composed of flattened cells are fairly common, making up possibly a third of the total, definite prickle cell keratinizing growths constitute a relatively small group. The dividing line between the two groups is, however, not sharp and this renders the classification of certain cases very difficult.

Classification According to Histogenesis.—Three sites of origin for primary carcinoma of the lungs are usually given: (1) the bronchial mucous membrane; (2) the bronchial mucous glands, and (3) the alveolar epithelium. The first two are generally spoken of as primary bronchial and the third as primary pulmonary tumors.

The primary bronchial tumors comprise the majority of cases and, according to many authors, the primary nodules are usually situated in the larger bronchi (Paessler,[7] Langhans,[4] Adler,[9] Wolff [19]).

The discussions of the histogenesis of lung tumors and of metaplasia of the epithelium of the lungs are inextricably interwoven, and accordingly an understanding of the changes in the lining epithelium of the respiratory tract, which may be broadly grouped under the term metaplasia, is essential. While there has been a prolonged discussion of the question of metaplasia, it is now generally conceded that this term does not imply a direct change of one cell into a cell of a different order, but a reversion of the formative cells of an epithelial tissue, so that their specificity is lost at the expense of regaining the powers of differentiation possessed by embryonic epithelial cells. The term false metaplasia and pseudo-metaplasia may be used to describe changes in form alone or a histological accommodation, as when the cylindrical cell lining of a cyst becomes flattened by pressure, undergoing mechanical changes only, and changes in the type of epithelium, really a

17. Watsuji, S.: Beiträge zur Kenntnis des primären Hornkrebses der Lunge, Ztschr. f. Krebsforschung **1**:445, 1904.

18. Ernst, P.: Ein verhornender Platten-epithelkrebs des Bronchus: Metaplasia oder aberration, Beitr. z. path. Anat. u. z. allg. Path. **20**:155, 1896.

19. Wolff, J.: Die Lehre von der Krebskrankheit, Jena, 1911, Part 2, p. 803.

substitution process, as is seen in the hornification of the cervix by the ingrowth of vaginal epithelium (Borst [20]).

By a study of cases of bronchopneumonia showing multiple foci of squamous cell metaplasia of the bronchial lining epithelium, Haythorn [21] has attempted to determine the mechanism through which these changes have occurred. He investigated each layer of the mucous membrane separately and concluded that the absence or the rarity of columnar cells and goblet cells precludes the probability of their taking part in the process, and concluded that the regeneration and transformation must take place from the cells of the formative layer. He stated, furthermore, that there was in no instance an example of stratified squamous epithelium resting on a well developed basement membrane. His conclusions included the views, that the metaplastic cells are produced by the formative layer of the mucous membrane, that the finding of multiple foci of squamous cells is against the idea of embryonic rests, and that there is suggestive evidence of a link between injury to the basement membrane, metaplasia, and the formation of new growths.

The proliferative changes in the epithelium of the lungs secondary to inflammatory reactions have been studied by many investigators (Kitamura,[22] McKenzie,[23] Haythorn [21]). The presence of squamous epithelium in tuberculous cavities and in the bronchi leading to them is a common observation. There are also many observations of similar changes distributed widely throughout the lungs in chronic or organizing bronchopneumonia, and McKenzie [23] has described these changes in acute bronchopenumonia. It might be noted in this connection, that a change from cylindrical epithelium to squamous epithelium associated with chronic inflammatory conditions is also seen in the gall bladder, pancreas, and in other organs. The change of alveolar epithelium in scars and of regenerating alveolar epithelium from a flat, pavement-like cell to a cuboidal or columnar type is important in understanding the histogenesis of lung tumors. The many other changes in epithelial cells associated with inflammatory processes are too well known to require a detailed description. Some of these changes, along with the striking pictures of epithelial regeneration seen in the recent influenza epidemic, will be referred to later.

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20. Borst, M.: Das pathologische Wachstum, Aschoff, L., Pathologische Antomie, Jena, **1**:41, 1919.

21. Haythorn, S. R.: On the Metaplasia of Bronchial Epithelium, J. M. Research **26**:523, 1912.

22. Kitamura, S.: Ueber secundäre Veränderungen der Bronchien und einige Bemerkungen über die Frage der Metaplasie, Virchows Arch. f. path. Anat. **190**:163, 1907.

23. McKenzie, I.: Epithelmetaplasie bei Bronchopneumonie, Virchows Arch. f. path. Anat. **190**:350, 1907.

Carcinoma Arising from the Bronchial Mucous Membrane.—These tumors are described as producing extensive changes in the bronchial mucosa advancing along the walls of the bronchi and septa, but seldom showing a diffuse involvement of the pulmonary parenchyma (Reinhard,[5] Ewing [24]). The bronchi may be filled with papillary projections over a wide area producing a thickening of the wall and invading the parenchyma. Obstruction to the bronchi and resulting bronchiectasis and atelectasis are not infrequently described. Small tumors arising in the walls of tuberculous cavities or appearing as nodular projections into the lumen of a bronchus, also undoubtedly take their origin from the epithelium of the bronchi.

The histologic characteristics of tumors arising from the bronchial mucosa have been variously described. Adler [9] says that they are of alveolar structure with polymorphous and polyhedric cells, for the most part flat, but that sometimes varying numbers of cylindrical cells are intermingled, while Ewing [24] states that cylindrical cells may be found in all forms of lung cancer, but that the presence of high cylindrical cells and their persistence in metastases is indicative of origin from the bronchial mucosa. He states, furthermore, that carcinoma may also arise from metaplastic bronchial epithelium giving a tumor of the squamous cell type.

The squamous cell tumors discussed in a preceding paragraph on histologic classification were first described as arising from the alveolar epithelium (Perls,[25] Fuchs,[11] Japha,[26] Grünwald,[27] Wolf,[6] Dömeny;[28] Edlavitch [29]), but the embryology of the pulmonary epithelium, the cubical form taken by cells of isolated alveoli in fibrous scars, and the appearance of regenerating alveolar epithelium, are against this view.

It is now generally conceded that the squamous cell tumors arise from the bronchial mucous membrane (Wolf,[6] Sehrt,[8] Ernst,[18] Watsuji,[17] Friedlander,[30] Hermann [31]). Two explanations of this occurrence have been proposed; (1) metaplasia of the normal epithelium, and (2) the embryonic displacement of islands of squamous cells. The

24. Ewing, J.: Neoplastic Diseases, Philadelphia, 1919, p. 785.
25. Perls, M.: Zur Kasuistik des Lungenkrebses, Virchows Arch. f. path. Anat. **56**:437, 1872.
26. Japha, A. F.: Ueber primären Lungenkrebs, Inaug. Diss., Berlin, 1892. (Quoted by Watsuji.[17])
27. Grünwald, L.: Ein Fall von primären Plasterzellenkrebs der Lunge, München. med. Wchnschr. **36**:548, 1889.
28. Dömeny, P.: Zur Kentniss des Lungen carcinoms, Ztschr. f. Heilk. **23**:407, 1902.
29. Edlavitch, B. M.: Primary Carcinoma of the Lung, J. A. M. A. **59**: 181 (July 20) 1912.
30. Friedlander, C.: Kankroid in einer Lungenkaverne, Fortschr. d. med. **3**:307, 1885.
31. Hermann, M.: Ein Fall von primären Cancroid der Lunge, Ztschr. f. Krebsforsch. **13**:446, 1913.

consensus of opinion is in favor of the first explanation. This is chiefly because of the fact that a conversion of the normal columnar cell lining into a layer of squamous cells in association with chronic inflammatory changes in the bronchi, is not infrequently seen. The second explanation was proposed by Siegert [32] who called attention to the fact that the anlage of the respiratory tract is a ventral outgrowth from the foregut, and suggested that squamous celled tumors of the lungs may develop from aberrant oesophageal epithelium. Peritz [33] called attention to the incorrectness of this idea in that during early embryonic life the esophagus is lined with ciliated cylindrical epithelium.

Carcinoma Arising from the Bronchial Mucous Glands.—A high percentage of the cylindrical cell tumors are attributed to this origin (Fuchs,[11] Kretschmar,[34] Wolf,[6] Langhans [4]). This view is apparently based on changes in the appearance of the bronchial mucous glands, on the glandular architecture of the tumors, and on the tendency of the tumor cells to secrete mucus. The tumor mass in typical cases is limited to the bronchial wall and the tissues immediately adjacent. The mucosa of the bronchus may be intact.

A classical example of this type was reported by Langhans.[4] There was extensive involvement of the bronchial tree. Just above and below the bifurcation of the trachea, the wall was thickened and elevated without ulceration of the overlying mucosa, but with extension into the peritracheal tissue. In the smaller bronchi there were also nodular elevations and a uniform infiltration of the wall, producing a narrowing of the lumen. Microscopically, alveoli, solid nests and strands of cells in a connective tissue background, were seen extending from the mucosa to the peribronchial tissue. These cell groups resembled closely the bronchial mucous glands. Langhans described a complicated glandular architecture and believed that different areas represented steps in the transition from the normal bronchial mucous gland to the cancerous alveoli. With this interpretation he described (a) enlargement of the glands up to eight and ten times the normal size with a single layer or many layers of lining cells to complete obliteration of the lumen; (b) extreme irregularity in the shape and size of the glands; (c) loss of the basement membrane; (d) numerous intercommunications between these large, irregular, glandlike spaces.

The conclusion that this tumor arose in the bronchial mucous glands was based on the absence of gross involvement of the bronchial lining epithelium, the extensive involvement of the bronchial wall, and the histologic resemblance to the normal glands.

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32. Siegert, F.: Ueber Primäre Geschwülste der unteren Luftwege, Virchows Arch. f. path. Anat. **129**:413, 1892.

33. Peritz, G.: Ueber Brusthöhlen Geschwülste, Inaug. Diss., Berlin, 1896. (Quoted by Watsuji.[17])

Carcinoma Arising from the Alveolar Epithelium.—Some authors have described squamous cell tumors as having this origin. However, a study of the development of the alveolar epithelium, which in the early stages is cuboidal or columnar, and, similarly, observations upon regenerating alveolar epithelium which is also cylindrical or cuboidal, are against this view. The consensus of opinion is that these tumors arising from the alveoli are not composed of squamous cells but of cells of the cylindrical or cuboidal variety. Kretschmar [34] has described a case which has been accepted generally by later investigators as of undoubted alveolar origin. In this case, there was extensive infiltration of the lung tissue, giving the gross appearance of an organizing bronchopneumonia. The tumor was definitely alveolar in structure, consisting of large alveoli lined with a single layer or many layers of high cylindrical cells. Some alveoli showed infoldings and papillary projections into the lumina, while in other places there was a more intricate branching structure. There were also extensive areas of necrosis with only faintly visible alveolar outlines. At the periphery there were a few alveoli showing a single layer of low cuboidal epithelium or several layers piled up to form small projections into the lumina. Kretschmar [34] interpreted this picture as the beginning of the process. In other places there were many irregularly arranged, large polygonal cells with very large nuclei.

The bronchi were filled with mucus and cellular detritus. The epithelial lining and membrane propria were for the most part intact. The bronchial mucous glands were hyperplastic. The submucosa contained nests of irregularly round, oval, or polygonal cells, having no connection with the mucous glands.

The diagnosis of alveolar origin of this tumor was based on the extensive involvement of the pulmonary parenchyma, the relatively slight involvement of the bronchial lining epithelium, the absence of any demonstrable connection with the bronchial mucous glands, and the resemblance to regenerating alveolar epithelium.

In discussing the alveolar origin of lung tumors, Paessler [7] stated that forty-seven of fifty-four reported alveolar tumors, or 87 per cent., were apparently of bronchial origin. Furthermore, he concluded that the morphologic characteristics of lung tumors are so variable that it is impossible to determine their histogenesis in the majority of cases.

RELATION OF IRRITATION TO NEOPLASTIC GROWTH

Chronic irritation of the respiratory tract has long been considered an important factor in the causation of lung tumors. Adler [9] calls

34. Kretschmar, W.: Ueber das primäre Bronchial und Lungencarcinom, Inaug. Diss., Leipzig, 1904.

attention to the much higher percentage of cases in men than in women, and suggests that this difference may be attributed to irritation from tobacco smoking. In many instances a preceding history of chronic bronchitis and bronchopneumonia is obtained, and many authors have called attention to this association. The marked epithelial overgrowth in bronchitis and bronchopneumonia, as well as the changes in the epithelium frequently seen in fibrotic areas, is suggestive, and Menetrier [35] and Ribbert [36] have suggested that lung tumors may arise in these areas.

The greatest emphasis has been placed on the association between tuberculosis and cancer of the lungs. Bayle [2] first described co-existent cancer and tuberculosis, and subsequently many observers have called attention to a similar association (Wolf,[6] Sehrt,[5] Perrone,[37] Friedlander.[30]) In thirty-one carcinomas of the lung studied by Wolf,[6] thirteen showed tuberculous lesions. He stated that bronchial carcinomas were usually found in places subjected to the greatest mechanical injury, that is, at the bifurcation of bronchi of various orders, where, on account of the angulation, irritation from dust or other inspired particles is greatest. His theory, often designated by the term "Pigmentdurchbruch," proposed that anthracotic tuberculous lymph nodes at these points rupture into the bronchi and thus acting as the source of a chronic irritant, lead to cancer. He described such lesions, but his ideas and work have not received support and confirmation. Friedlander,[30] Perrone,[37] Wolf,[6] Kaminsky,[38] Neumeister,[39] and Gougerot [40] have described squamous cell carcinoma, and Schwalbe [41] a cylindrical cell carcinoma arising in the walls of tuberculous cavities.

CASE REPORTS

CASE 1.—*Clinical History.*—J. P., a white female, aged 67 years, was admitted to the New Haven Hospital, May 27, 1918, in an unconscious condition. The family history was irrelevant. The personal history revealed the fact that the patient had suffered from a cough and bronchitis since childhood. The

35. Menetrier, P.: Cancer primitif du poumon, Prog. méd. **3**:436, 1886.

36. Ribbert, H.: Bemerkungen zu einem Falle von primären Lungencarcinom., Deutsch. med. Wchnschr. **22**:165, 1896.

37. Perrone, A.: Entwicklung eines primären Kankroids von der wand einer tuberculosen Lungenkaverne, Arb. a. d. path. Inst. zu Berlin, Feier. J. Orth. 1906, p. 235.

38. Kaminsky, M. M.: Ueber primären Lungenkrebs, Inaug. Diss. Greifswald, 1898. (Quoted by Perrone.[37])

39. Neumeister, K.: Ein Fall von primären Plattenepithelkarzinom der lunge mit metastase im Schultergelenk, München. med. Wchnschr. **52**:1721, 1905. (Quoted by Perrone.[37])

40. Gougerot, H.: Cancer primitif du poumon á globes épidermique, Bull. et mém. Soc. anat. de Par. **80**:294, 1905. (Quoted by Perrone.[37])

41. Schwalbe, E.: Entwickelung eines primären Carcinoms in einer tuberculosen Caverne, Virchows Arch. f. path. Anat. **149**:329, 1897.

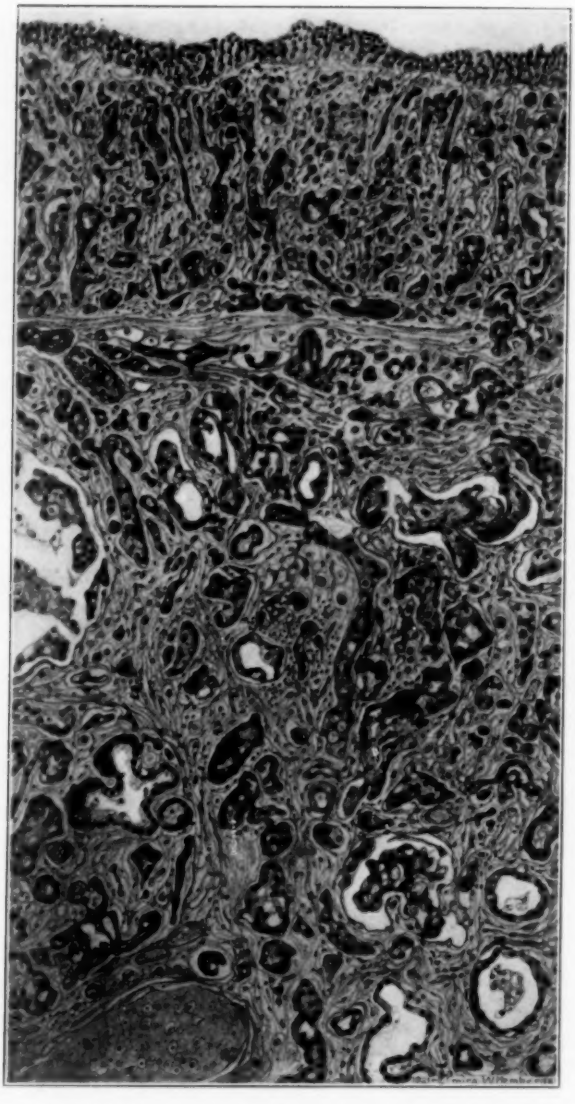

Fig. 1.—Case 1. Microscopic drawing of a peribronchial tumor nodule. The bronchial wall is thickened. The tumor forms solid nests of epithelial cells resembling the overlying metaplastic mucous membrane and numerous glandular alveoli suggesting the bronchial mucous glands.

present illness was completely dominated by symptoms of cerebral hemorrhage. The examination was confirmatory of this condition. The patient did not recover consciousness and died about nine hours after admission.

Necropsy 59 (Performed by Dr. McKinlay about twelve hours after death): *Anatomic Diagnosis.*—Carcinoma of the bronchus; multiple metastases to the lungs, heart muscle, hilic and retroperitoneal lymph nodes, suprarenals, and thyroid. Subsidiary. Chronic mitral and aortic verrucose endocarditis; cardiac hypertrophy and dilatation; cholelithiasis; chronic cholecystitis and fibrous pericholecystitis; encapsulated tuberculous lymphadenitis.

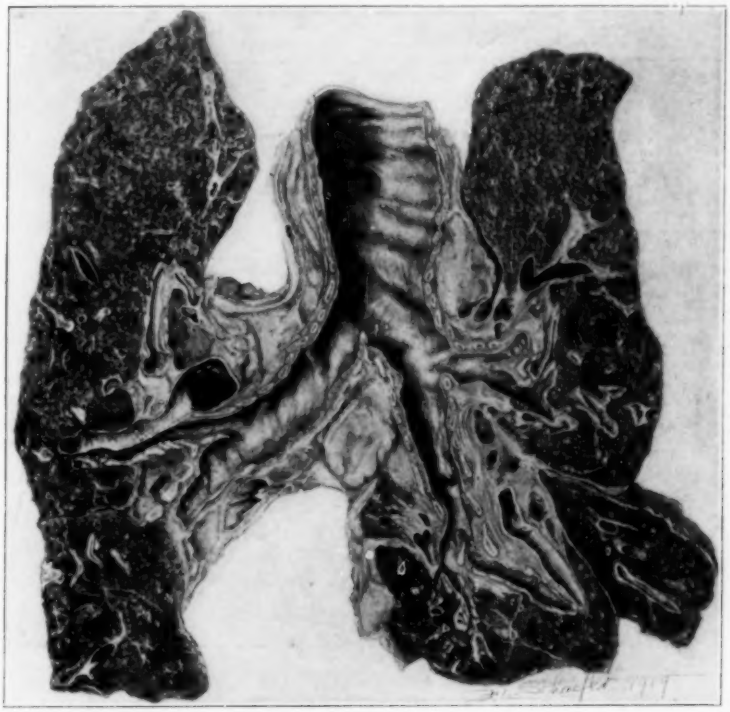

Fig. 2.—Case 2. Primary carcinoma of the bronchus (posterior view). The primary tumor is shown projecting into the lumen of the bronchus to the right lower lobe just beyond a point of bifurcation. The tumor surrounds the larger bronchi in the right lung and fills the angle beneath the tracheal bifurcation. The hilic and peritracheal lymph nodes on both sides are involved but there are no tumor nodules in the left lung.

Protocol.—(Abstract.) The body is that of a fairly well nourished female, measuring 155 cm. in length and weighing 112 pounds. Rigor mortis is present. There is marked postmortem lividity of the back. The pupils are equal and regular and the conjunctivae are pale. The thorax is flat. The abdomen is distended. The peritoneal surfaces are everywhere smooth and glistening and there is no excess of fluid. The liver extends 10 cm. below the costal margin in the right midclavicular line. The left pleural cavity contains about 100 c.c.

of clear straw colored fluid. There are a few fibrous adhesions between the parietal and visceral pleurae over the lateral aspects of the upper lobe. The right pleural cavity contains about 300 c.c. of clear straw colored fluid. The pericardial sac presents nothing abnormal.

Lungs: There are small white, fibrous scars at both apices. There are also numerous fibrous tags on the pleural surfaces. The lungs crepitate throughout but have a nodular consistence with areas of emphysema at the periphery of the lobes. The cut surface of the lungs appears red in color, and is mottled with black pigmented areas. Throughout the lungs the blood vessels and bronchi are prominent on account of the surrounding grayish-white areas which vary from narrow rims to broad bands extending as much as a centi-

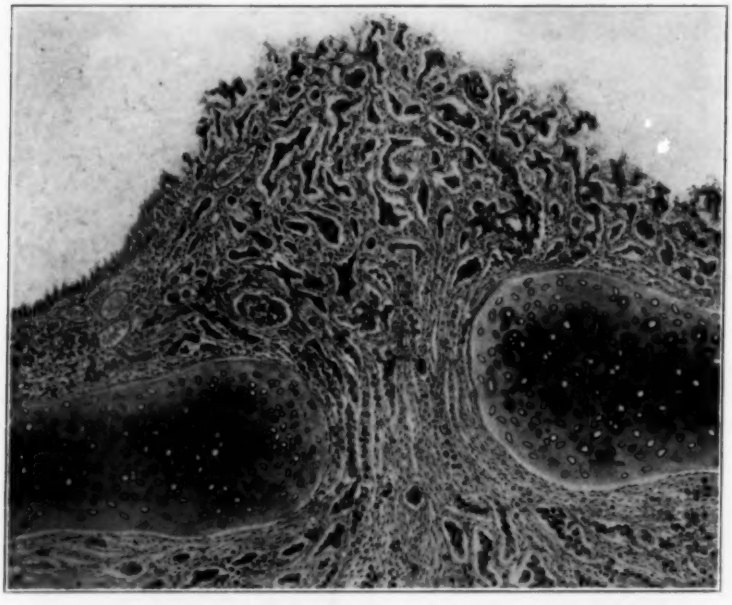

Fig. 3.—Case 2. Microscopic drawing of the primary bronchial tumor shown in Figure 2. The hyperplastic surface epithelium is seen on the left of the drawing. The nests of carcinoma cells extend along the free surface and throughout the bronchial wall. These cell nests resemble the proliferated bronchial epithelium seen in influenza (compare Fig. 15).

meter into the surrounding tissue. These areas are firm in consistence and grayish-white in color. The condition is somewhat more marked in the right lung. The hilic lymph nodes are markedly enlarged, some measuring 3 cm. in diameter. The cut section appears grayish-white in color. Some are translucent and others are opaque in appearance and on pressure a white mucoid material exudes from the centers.

Metastases: There are tumor nodules in both suprarenal glands, the retroperitoneal, mediastinal and the hilic lymph nodes. These nodules resemble the tumor in the lung. The gross findings in the other organs have no relationship to the tumor and will not be described.

Microscopic Notes.—Lungs: The lungs present several interesting findings. The first is the tumor. There are numerous circumscribed carcinoma nodules situated chiefly in the peribronchial region (Fig. 1). They are composed of a fibrous background within which numerous small, irregularly shaped, solid masses and strands of epithelial cells are seen. These cell nests extend through the submucosa, reaching up to, and almost encroaching on, the mucous membrane. The cells are large and polyhedral in shape with large nuclei. The nuclei vary greatly in size, shape, and chromatin content. They vary from the deeply pyknotic to clear vesicular nuclei with large central nucleoli. Mitotic figures are numerous. The cells resemble normal squamous epithelium but there are no epithelial whorls or areas of keratinization. In many areas the overlying bronchial mucous membrane is metaplastic and forms numerous layers of stratified epithelium. There is no definite basement membrane and there are areas suggesting a continuity between the tumor and the

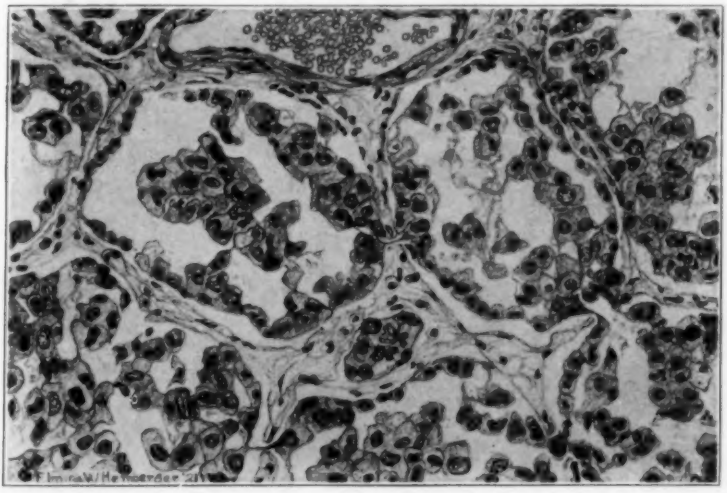

Fig. 4.—Case 2. Microscopic drawing showing area in which the tumor has invaded the air spaces. The masses of tumor in adjacent alveoli are connected through openings in the alveolar walls. The tumor cells fill the lumina or extend along walls of the alveoli.

metaplastic mucosa. The resemblance between the tumor cells and the cells of the overlying mucous membrane is striking. However, in other areas a different picture is seen. There are areas of carcinomatous alveoli of varying form and size. Some are lined with a single layer of columnar epithelium and a few are histologically indistinguishable from the normal bronchial mucous glands. Others are markedly irregular in size and shape, showing infoldings and outgrowths of the lining cells with all gradations to the solid masses. In some places mucous secretion is evident. The other findings of interest are evidences of a preceding organizing inflammatory process and the changes in the alveolar epithelium. There are numerous organized thrombi, areas with definite thickening of the alveolar walls and fibrotic areas in the perivascular and peribronchial regions in sections free from any tumor. There are also areas in which the alveolar epithelium is distinctly cuboidal and occasionally forms several layers. This is most conspicuous in the scarred areas.

Metastases:[42] There are numerous cancer emboli in the vessels of the myocardium. The suprarenals and the thyroid show tumor nodules with a structure similar to that of the primary tumor in the lungs. In some areas the cells resemble those of metaplastic bronchial epithelium. The lymph nodes show a similar type of tumor, as well as areas in which the cells are arranged irregularly in a loose meshwork.

Summary.—The history of bronchitis in early life and the presence, at necropsy, of widespread areas of organization in the lungs are evidences of the existence of a preceding organizing inflammatory process. There was marked variation in the histologic characteristics of this tumor with areas

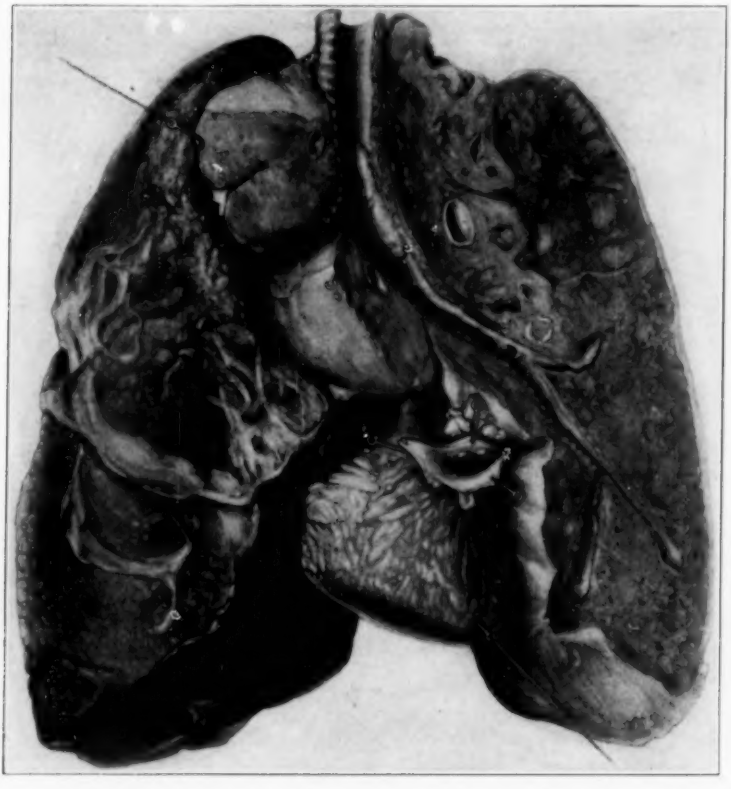

Fig. 5.—Case 3. Carcinoma of the bronchus (gross drawing). The primary tumor is seen filling the first branch of the main bronchus to the left lung. There is extensive infiltration of the left lung. Tumor nodules are seen within the pericardium and the right auricle. There is an oval mass of tumor projecting into the trachea at the bifurcation and a large mass filling the mediastinum.

42. The history suggests cranial metastases, but this could not be determined as permission for an examination of the head was not obtained.

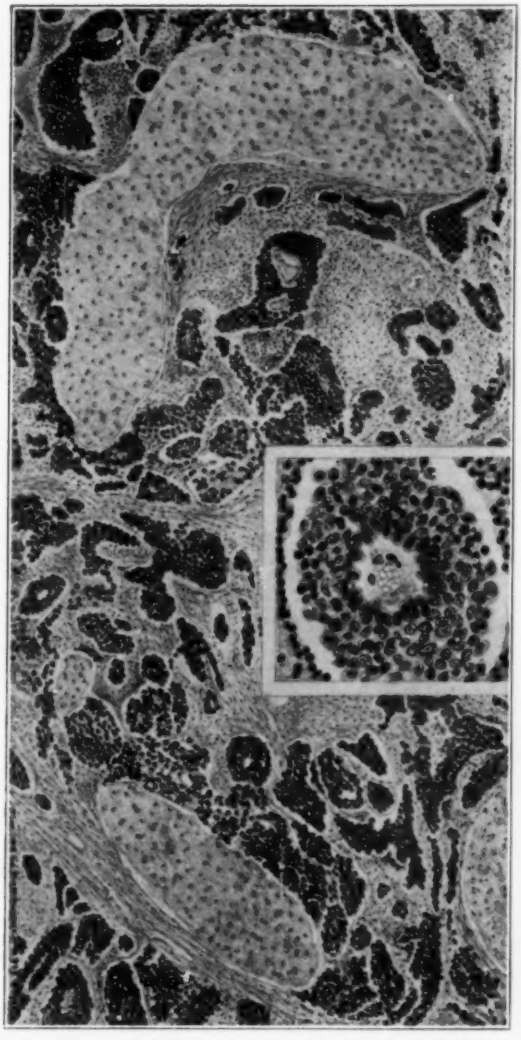

Fig. 6.—Case 3. Microscopic drawing of a section through plugged bronchus (primary tumor) showing islands of cancer cells which in many places surround small blood vessels. There are extensive areas of necrosis and fibrosis. This picture is uniform throughout the tumor.

resembling the metaplastic bronchial mucous membrane, as well as areas suggesting the bronchial mucous glands. The metastases were of widespread distribution and resembled the peribronchial nodules. The exact location of the primary site was not determined and a question might be raised concerning the bronchial origin of this tumor. However, there was no evidence, grossly or microscopically, of a primary tumor in any other organ, although a careful search was made. The tumor nodules within the lungs were confined to the peribronchial area, a lymphatic distribution, which is in favor of a primary rather than a secondary tumor. While the bronchial origin cannot be conclusively proved a consideration of the case as a whole shows that the evidence is undoubtedly in favor of this diagnosis.

Case 2.—*Clinical History.*—G. K., a white male, aged 60 years, was admitted to the New Haven Hospital, Feb. 22, 1919, complaining of breathlessness, cough

Fig. 7.—Case 4. Primary carcinoma of the bronchus (gross drawing). The external view shows a depressed scar on the surface of the left upper lobe. Small secondary tumor nodules are seen on the pleural surface. The cross section shows the primary tumor just beneath the depressed area on the surface. The tumor had its origin in a small bronchus just peripheral to the point of bifurcation.

and pain in the back. The family history and personal history are unimportant. The present illness began about three months before admission with pain in the back and girdle pains about the waist. During this time he has also suffered from gradually increasing dyspnea. For the last three weeks he has had a severe cough with considerable expectoration and has been unable to sleep well on account of orthopnea.

Physical Examination.—The patient was considerably emaciated and was breathing with some difficulty. The cervical lymph nodes were slightly enlarged. There was a firm, bony, hard mass just above the left clavicle and a small nodule on the third rib just to the right of the sternum. The chest was emphysematous in type. In front the percussion note was hyperresonant except for slight impairment at the right apex. At the right apex and just below the right clavicle the sounds were bronchial; elsewhere the breath sounds were harsh. There was marked dulness and the breath sounds were distant over the entire right back. On the left, the percussion note was slightly hyperresonant and the respirations were harsh. The heart showed nothing of importance. The liver edge was palpable two fingers' breadth below the right costal margin.

The patient died suddenly on the evening of Feb. 23, 1919.

Necropsy 204 (Performed by Dr. McNamara about ten hours after death): *Anatomic Diagnosis.*—Carcinoma of the bronchus; invasion of the lung; metastases to the regional, cervical, retroperitoneal and mesenteric lymph nodes, suprarenals, pancreas and kidneys; invasion of cancer into the wall of the vena cava; ascites; occlusion of bronchus; local pulmonary atelectasis; hydrothorax; cancer thrombi in the pulmonary vessels; *propagated pulmonary thrombus (stem of pulmonary artery).* Subsidiary: Apical pulmonary scars; hydrocele.

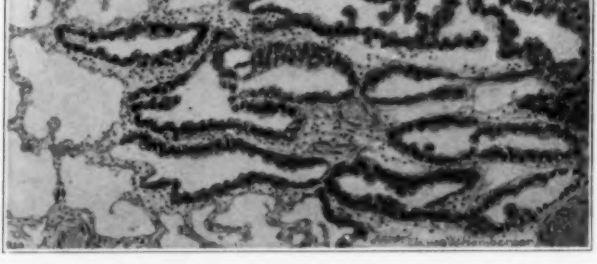

Fig. 8.—Case 4. Microscopic drawing of primary tumor of bronchus. The section is taken from the periphery of the primary tumor. There is a resemblance to regenerative alveolar epithelium and to tumors described as arising from the alveolar epithelium.

Protocol.—(Abstract.) The body is that of a poorly nourished white male weighing 156 pounds and measuring 170 cm. in length. There is a firm mass just above the inner end of the left clavicle and a firm nodule adherent to the third rib just to the right of the sternum. On section this nodule is pearly gray and translucent in appearance and does not invade the rib. The abdominal wall, the back, the scrotum and the extremities are definitely edematous. The peritoneal surfaces are everywhere smooth and glistening and the cavity contains about 350 c.c. of clear, straw colored fluid. The edge of the liver extends 15 cm. below the tip of the xiphoid and 11 cm. below the costal margin in the right midclavicular line. There is a firm nodular tumor about the size of a lemon, in the region of the head of the pancreas. The mesenteric and retroperitoneal lymph nodes are enlarged.

The right pleural cavity contains about 2,000 c.c. of clear straw colored fluid and the lung is collapsed. The left pleural cavity contains no fluid. There

are a few fibrous adhesions at both apices. The anterior mediastinal tissues are edematous. The pericardial cavity contains about 100 c.c. of a blood tinged fluid. The serous surfaces are smooth and glistening.

Heart: The right side of the heart and the pulmonary artery are greatly distended while the ascending portion of the aorta is collapsed. After making an incision into the right ventricle and extending it into the pulmonary artery, a large thrombus is seen filling both branches of the pulmonary artery and extending back to the pulmonary valve. The remainder of the heart shows nothing abnormal.

Lungs: There are apical scars and a few fibrous adhesions in this region as well as over the lateral and posterior portions of the upper lobes of both lungs. The right lung is small in volume due to compression by the large pleural effusion. Externally, the lungs show no other abnormalities. On

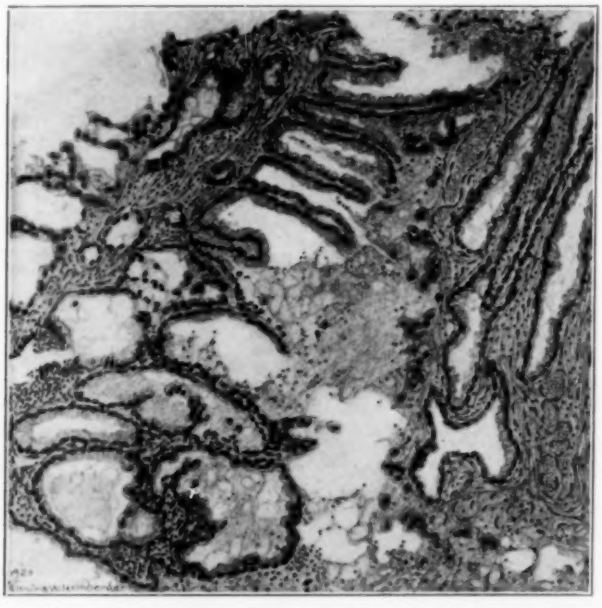

Fig. 9.—Case 4. Microscopic drawing of a section of the primary nodule. The carcinomatous alveoli resemble normal bronchial mucous glands with a tendency to formation of papillary ingrowths. Mucous secretion is marked. The picture conforms to the description of tumors arising in the bronchial mucous glands.

palpation there is a large, sharply localized, firm mass in the right lower lobe near the hilum. A frontal section, dividing the trachea, bronchi and lungs, reveals an interesting condition. A striking feature is the prominence of the thrombi which protrude from the arterioles over the entire surface. The tracheal mucosa is quite normal. In the main bronchi the mucosa is smooth, but intensely injected. Just below the bifurcation of the bronchus to the right lower lobe, there is an abrupt change. A firm mass with an irregularly raised surface is seen practically occluding the lumen for about 1.5 cm. (Fig. 2). Below this mass, there is a similar change back to the normal

mucosa. The terminal portion of the bronchus is dilated. This nodule is probably the primary site. The configuration of the invasion of the lung is beautifully seen. The peribronchial and perivascular regions are everywhere outlined by encircling bands of tumor which become more and more conspicuous as the hilum is approached. This pathway leads to a large mass in the angle beneath the tracheal bifurcation, and can be traced up through the mediastinum to the left supraclavicular region. The hilic glands on the left are also involved, but numerous sections show no metastases in the left lung.

Metastases: The right kidney and the suprarenals show tumor nodules. There is a firm tumor mass, apparently composed of enlarged lymph nodes, near the head of the pancreas. This mass also extends into the substance of

Fig. 10.—Case 4. Microscopic drawing of metastasis in ovary. The resemblance to a small bronchiole is striking.

the pancreas. The cervical, hilic, mesenteric and retroperitoneal lymph nodes contain metastases. The retroperitoneal lymph nodes compress the vena cava and its tributaries, and just above the junction of the iliac veins there is a tumor nodule projecting into the lumen of the vena cava. There are also several areas of partial atrophy of the wall of the vena cava as the result of pressure by the carcinoma nodules. These metastases resemble the primary tumor.

Microscopic Notes.—Lungs: At the periphery of the primary tumor, the mass projects into the main bronchus to the left lower lobe; the bronchial mucosa varies from the normal to several layers of hyperplastic epithelium.

The cells are somewhat irregularly arranged and are many layers deep, but vary only slightly from the usual cylindrical lining cells. The central portion shows complete loss of the mucous membrane with cancer cells extending along the free surface (Fig 3). The cells form irregular strands and solid nests invading the bronchial wall extensively and extending in either direction in the submucosa between the cartilages and into the peribronchial tissue. The cells are somewhat polymorphous and their arrangement suggests squamous epithelium. There are no epithelial pearls or areas of keratinization. The cells are large and the nuclei vary greatly in chromatin content. Mitotic figures are numerous. The resemblance of these cells to the bronchial epithelium is suggestive and immediately recalls the islands of proliferated bronchial epithelium observed in the recent influenza epidemic.

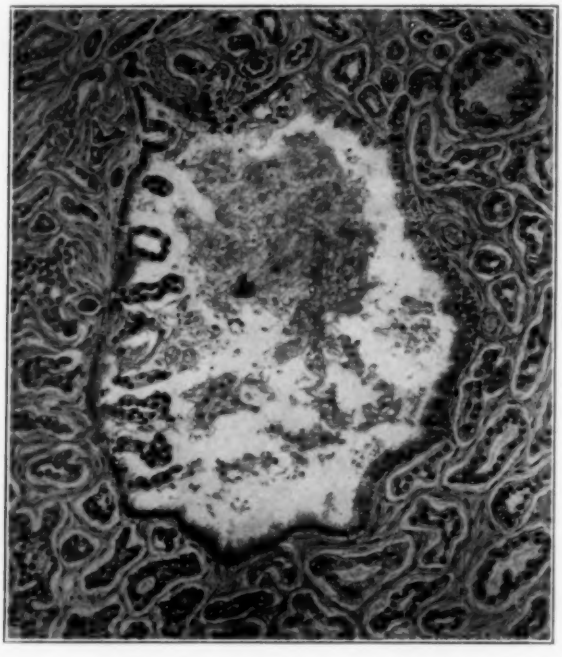

Fig. 11.—Case 4. Microscopic drawing of small bronchus with surrounding carcinoma. The carcinoma cells are seen pushing through the wall into the lumen of the bronchus.

In neighboring areas, however, the bronchial mucous glands are hyperplastic and there are changes present which suggest that they may be participating in the neoplastic growth. The comparative uniformity of the tumor elsewhere is against this suggestion despite the apparent hyperactivity of the glands, and the changes are probably only secondarily related to the tumor. In other sections the alveolar epithelium is distinctly cuboidal and in some alveoli is piled up to form several layers.

In the surrounding lung the alveoli are filled with solid nests of tumor cells. These cells likewise form syncytial masses and irregular alveoli. There are

many areas in which the carcinoma cells extend through the alveolar walls forming figures resembling closely the fibrin molds of the alveoli extending through the so-called pores of Cohn frequently seen in the pneumonic lung (Fig. 4). The cancer cells also extend along the alveolar walls replacing the lining epithelium. In some areas it is difficult to differentiate tumor cells growing along the alveolar walls from regenerating alveolar epithelium. In addition to the tumor masses in the alveolar spaces there are peribronchial and perivascular nodules and tumor cells are seen within many of the blood vessels and lymphatics. There are nodules extending to the pleura but not invading it. The lymphatic channels of the interlobular septa contain many cancer cells. Large polyhedral cells predominate but many cuboidal and flattened, pavement-like cells are present. The nuclei are large and numerous mitotic figures are present. The cytoplasm is finely granular. In many places several nuclei are seen in an undifferentiated mass of cytoplasm.

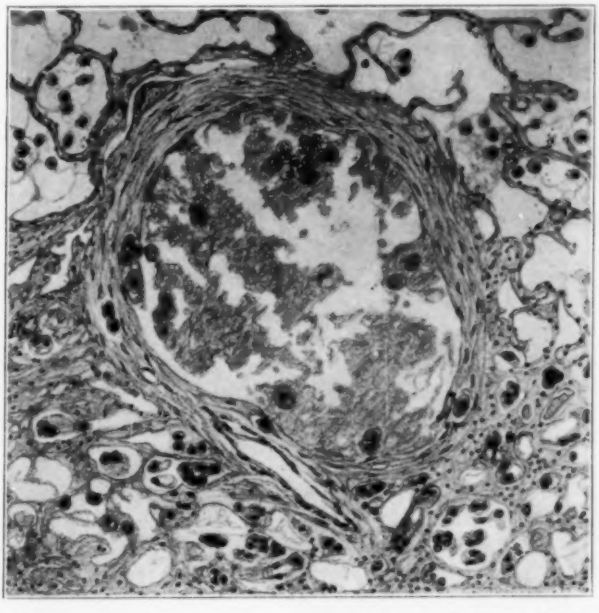

Fig. 12.—Case 4. The drawing shows carcinoma cells in the wall and within the lumen of a small pulmonary blood vessel.

In all sections the blood vessels are conspicuously congested and in some there are fresh as well as organizing thrombi. In some areas there is a hemorrhagic exudate in the alveolar spaces. There are numerous areas of peribronchial and perivascular fibrosis. There is no evidence of tumor in the left lung although the fresh and organizing thrombi as well as the fibrotic peribronchial and perivascular areas are present.

Metastases: The suprarenals, the right kidney and the cervical, retroperitoneal and mesenteric lymph nodes show metastases resembling the tumor in the lung.

Summary.—There were widespread areas of peribronchial and perivascular organization as evidence of a preceding organizing inflammatory process. The

tumor was largely situated in the peribronchial and perivascular regions, but there was also invasion of the pulmonary parenchyma.

The majority of the tumor cells formed strands and solid nests of polymorphous cells but there were some areas showing a glandular structure. The metastases were of widespread distribution and resembled the primary tumor. The tumor was undoubtedly of primary bronchial origin, and probably began in the nodule projecting into the main bronchus to the right lower lobe.

Case 3.—*Clinical History.*—I. M., a white male, aged 39 years, was admitted to the New Haven Hospital, Oct. 4, 1919, complaining of swelling of the left

Fig. 13.—Case 5. Primary carcinoma of the bronchus (posterior view). The tumor involves the lower portion of the trachea and both main bronchi with widespread invasion of the right lung and bronchial lymph nodes. The probable point of origin, in first bronchus to the right upper lobe does not appear in this section (see text).

arm. The history is meager as the patient spoke very little English. The patient has had cough with expectoration for five years and has had slight hemoptysis during the past year. He has had no night sweats. About Sept.

20, 1919, he began to suffer from pain in the right upper part of the chest radiating over the left shoulder and down the arm. This arm has gradually become swollen and the pain has decreased.

Physical Examination.—The physical examination showed evidence of an intrathoracic tumor. There was no precordial pulsation or tracheal tug. There were enlarged axillary lymph nodes on the left side with swelling of the shoulder and arm and evidence of a well developed collateral circulation in this region. There was a myosis of the left pupil, ptosis of the left eyelid, and paralysis of the left vocal cord. There was impairment of the percussion note over the entire left chest with bronchial breathing over a wide area.

Clinical Diagnosis.—Neoplasm of left upper lobe of lung, probably carcinoma.

The patient manifested difficulty in breathing which gradually became more marked until death on Nov. 11, 1919.

Necropsy 269 (Performed by Dr. Alter about four hours after death).—*Anatomic Diagnosis.*—Carcinoma of the bronchus; invasion of the left lung, mediastinum, pericardium and left auricle; occlusion of bronchus; chronic

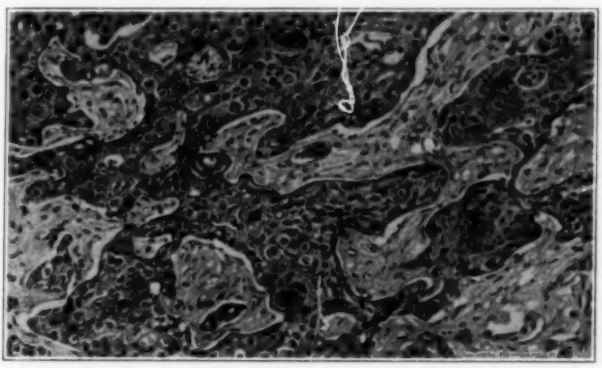

Fig. 14.—Case 5. Microscopic drawing of tumor in left lung. The tumor is a typical keratinizing squamous celled carcinoma.

tubular bronchiectasis; organized lobar pneumonia; fibrous pleurisy; compression of the aorta; organized thrombi in the axillary veins; edema of arm; emaciation.

Protocol.—(Abstract.) The body is that of an emaciated white male, measuring 162 cm. in length and weighing 105 pounds. Postmortem lividity and rigor mortis are absent. The trachea shows deviation to the left side and is firmly fixed. The supraclavicular glands are enlarged and firm. There is nothing of note in the abdominal cavity. The mediastinum is filled by a large, yellowish-white mass which is firmly adherent to the anterior thoracic wall and seems to extend up from the left lung. The left pleural cavity is completely obliterated. There are extensive adhesions between the parietal and visceral pleurae on both sides. The heart is pushed downward and to the left. After removing the lungs with the neck organs by dissecting the parietal pleura from the chest wall, only a relatively small amount of tumor remains attached to the bony structures surrounding the thoracic aperture. The trachea is virtually embedded in the tumor mass. The axillary veins form solid cords and on section are filled with organizing thrombi.

Lungs: The mediastinal organs are embedded in the large mass which measures about 13 cm. in its greatest diameter (Fig. 5). A transverse section through the left lung shows the distribution of the neoplasm. It extends upward along the trachea, surrounding and compressing the aortic arch and filling the mediastinal space. Downward it extends along the bronchi and

Fig. 15.—(Necropsy 183). Microscopic drawing of the proliferative changes in the bronchial epithelium in influenza. There is a partial obliterative bronchiolitis and organization of the surrounding lung tissue. The bronchial epithelium is several layers thick and has invaded the surrounding organizing tissue, giving the picture of an early carcinoma.

the larger vessels, into the lung along the ramifications of the vessels and bronchioles which stand out as thick walled tubes. It likewise extends along the larger vessels into the pericardial sac forming a polypoid mass around the pulmonary vessels. It invades the heart wall and projects into the cavity of

the left auricle as small, knoblike growths. The tumor projects into the bronchi in many places, apparently by extension from adjacent tumor nodules. The bronchial walls are thick; they are lined by a red, inflamed mucous membrane and contain a large amount of purulent material. In the upper and middle portions of the lung, there are numerous tumor nodules varying greatly in size. Just beyond the bifurcation of the main bronchus to the left lung, there is a mass, apparently the oldest portion of the tumor, surrounding, filling and completely occluding the lumen. This is probably the primary site. There is an elongated, oval mass, 5 cm. in length, projecting into the lumen of the trachea for about 1 cm. It extends up from the subjacent tumor mass and its surface is smooth and covered with epithelium. Many of the larger bronchi are somewhat compressed by the surrounding tumor. On section the larger masses resemble a rapidly growing medullary carcinoma with many areas of necrosis. The smaller masses are grayish-white in color and translucent in appearance.

The lower lobe is the site of an extensive inflammatory process. Only narrow areas are air-containing. The bronchi are somewhat compressed, but not obstructed, and can be followed to the periphery where they end in cylindrical dilatations. They are filled with necrotic brown débris.

The right lung is uninvolved and there are no metastases outside of the thoracic cavity.

Microscopic Notes.—Lungs: The sections through the primary site show some distortion of the cartilages by the surrounding growth (Fig. 6). The lumen is obliterated by the neoplasm. The tumor cells are best preserved around the blood vessels where they form round or irregular concentric nests surrounded by areas of necrosis or fibrosis. Radiating from the central vessel, there is an inner row of cylindrical cells surrounded by other cells irregularly arranged and closely packed together so that the shape of individual cells is less definitely discernible. The nuclei are relatively large and show many mitotic figures. There is no intercellular stroma.

With minor variations, this structure prevails throughout the tumor. There are a few areas in which long strands of cylindrical cells are present and many areas showing large masses of irregularly arranged cells. In the lung proper, there are areas in which the alveolar spaces contain masses of tumor cells. These areas are poorly preserved. In some places tumor cells extend through the alveolar walls connecting the tumor masses in neighboring alveoli, as was described in Case 2.

Sections from the lower lobe show an extensive organizing process with numerous bronchiectatic dilatations. There are areas of thickening of the alveolar walls with all gradations to completely fibrosed areas. The alveolar spaces are totally or partially obliterated and the lining epithelium is composed of a single layer or several layers of cuboidal cells. There is organization in areas distant from tumor nodules and portions of the lungs reached by compressed bronchi.

Microscopic examination of the other organs shows nothing of importance in connection with the tumor.

Summary.—The extensive organization was undoubtedly due to compression of the bronchi. However, there were changes, areas of organization distant from portions of the lung reached by compressed bronchi, indistinguishable from those seen in late cases of influenza, and there is little, if any, doubt concerning the existence of a preceding organizing inflammatory process. The history also confirmed this view. The distribution of the tumor was entirely within the thoracic cavity. The right lung was uninvolved. The left lung showed a tumor of peribronchial and perivascular distribution with many areas of invasion of the pulmonary parenchyma. The histological picture was uniform throughout, showing high cylindrical cells frequently arranged in irregular perivascular rosettes. There is no doubt concerning the bronchial

origin of this tumor, and there is presumptive evidence that the site of the origin was in the first left bronchus.

CASE 4.—*Clinical History.*—G. B., a white female, 42 years old, was admitted to the New Haven Hospital, Oct. 10, 1919, complaining of pain in the right knee and leg, cough, soreness in her chest, and blindness in the left eye. The family history shows that her father died of cancer of the liver, a paternal aunt of cancer of the breast, and her paternal grandfather of cancer of the stomach. The patient's sister had a kidney removed for a growth, the nature of which is not known. The personal history reveals an attack of dry pleurisy at the age of 16 years, a severe cough lasting several months at the age of 25 years, and a definite attack of influenza in March, 1919.

The present illness began in June, 1919, with a cough. At the same time she had pain in her right thigh and knee and some weakness in her legs. In August she developed diplopia, followed a week later by complete blindness in the left eye. In September she began to suffer from dyspnea and severe paroxysms of coughing associated with vomiting and occasionally with blood tinged sputum. There have been no night sweats. While in the hospital she became blind in the right eye.

Physical Examination.—The physical examination showed evidence of a malignant tumor with metastases in the left lung, the liver, the cranium, the ribs, and a generalized involvement of the lymph nodes. A lymph node was removed for diagnosis and showed an adenocarcinoma. On account of a mass felt in the region of the right kidney a clinical diagnosis of adenocarcinoma, probably primary in the right kidney, was made.

Necropsy 272 (Performed by me about three and one-half hours after death). —*Anatomic Diagnosis.*—Carcinoma of the bronchus with invasion of the lung; generalized metastases, including lymph nodes, bones, adrenal, ovary and liver; cancer emboli in the pulmonary artery; infarcts of lung; emaciation.

Protocol.—(Abstract.) The body is that of a markedly emaciated white female, measuring 172 cm. in length and weighing 95 pounds. Rigor mortis is not present. There is slight postmortem lividity of the back. There is a definite protrusion of the left eyeball. The pupils are equal and regular, measuring 5 mm. in diameter. There is a palpable mass in the right supraclavicular region and a small nodule in the left inguinal region. The peritoneal surfaces are everywhere smooth and glistening. The liver edge extends 6.5 cm. below the xiphoid process and 4 cm. below the costal margin in the right midclavicular line. There are numerous nodules along the edge of the liver. The pleural surfaces are everywhere smooth and glistening. There are several small, hard nodules firmly adherent to the ribs on the right side.

Lungs: Externally, there is a sharp line of demarcation between the lower portion of the left upper lobe, which is firm in consistence and dark reddish purple in color, and the remaining lighter colored, normal appearing lung (Fig. 7). Near the edge of this area, bordering on the interlobar fissure, there is a horizontal scar about 4 cm. in length. The scar is puckered and the center is depressed. On the surface there are numerous small, pea sized, elevated nodules. A section through the center of the scar shows a small mass about 1.5 cm. in diameter which is in all probability the primary nodule. It is firm in consistence, grayish-yellow in color, and of an irregular rosette shape. A small bronchus runs into the mass just after bifurcating. The surrounding lung tissue is firm and dark except for numerous white bands outlining the interlobular spaces and surrounding the bronchioles. The darker areas have a homogeneous smooth, waxy appearance. There is a sharp line of demarcation similar to that described on the surface. The remainder of the lung shows a widespread infiltration of the tumor. The distribution is chiefly in the peribronchial and perivascular areas where gravish-white bands are seen forming collars, around the bronchi and vessels, which become progressively larger as the hilum is approached. In several places the growth has invaded the bronchi, forming nodular projections into the lumina with or without

ulceration of the mucous membrane. The right lung is normal in appearance, except for two small infarcts at the lower margin of the upper and lower lobes respectively. The hilic glands on both sides are enlarged and lead to a large mass filling the angle beneath the bifurcation of the trachea.

Metastases: The liver contains numerous tumor nodules scattered over the surface and throughout the substance. The suprarenals and ovaries also contain small white tumor masses. There is a chain of carcinomatous lymph nodes involving both sides of the neck and extending through the mediastinum into the retroperitoneal and pelvic nodes. The mesenteric, inguinal, and axillary nodes also are involved. On section these metastases appear as firm, white, translucent nodules resembling the tumor in the lung. There are also several firm nodules on the ribs and on the inner table of the cranial vault, as well as a diffuse infiltration of the floor of the anterior fossa of the base of the skull with extension along the optic nerve into the retrobulbar space.

Microscopic Notes.—Lungs: The sections show a small bronchus extending into the proximal side of the primary nodule. The tumor fills the lumen of the bronchus and grows out peripherally spreading into a fan-shaped mass. The cartilaginous rings are somewhat distorted. In the proximal portion of the section the tumor is composed of numerous irregularly arranged cells with wide areas of necrosis. The central portion of the nodule shows a large amount of fibrous tissue with small alveoli or islands of epithelial cells. In the peripheral portion of the nodule, the following pictures are seen. (1) There are areas showing large and small alveoli lined with a single layer or many layers of cylindrical cells showing infoldings and papillary projections into their lumina. There are all gradations from simple alveoli lined with a single layer of cuboidal epithelium, to complicated intercommunicating alveoli with numerous infoldings and branching structures projecting into the lumina (Fig. 8). (2) There are areas best described by saying that they resemble closely the bronchial mucous glands showing all of the gradations from an alveolus resembling the normal gland, to complicated branching forms covered with mucous secreting cells (Fig. 9). Furthermore, the metastases, particularly in the lungs, also show areas resembling the bronchial mucous glands. (3) There are other areas showing polymorphous spaces lined with high cylindrical cells resembling the bronchial lining epithelium. This is even more striking in the metastases, particularly in the ovary where the resemblance to the smaller bronchi is vivid (Fig. 10).

One section shows a bronchiole surrounded by many irregular alveoli and nests of cancer cells which have invaded the submucosa and the mucosa, and are seen pushing into the lumen as irregular shaped papillae and alveoli (Fig. 11). In many sections of the lung, cancer cells are seen within the lumina and the walls of blood vessels (Fig. 12). Many alveoli are filled with large polymorphous cells with large nuclei, and in some places many nuclei are seen within an irregular shaped mass of undifferentiated protoplasm. In some areas the cancer cells, in adjacent alveoli, are connected by extension through the alveolar walls as was described in Cases 2 and 3. In other areas the cancer cells extend along the alveolar walls, appearing as large polyhedral, cuboidal or flattened pavement-like cells replacing the alveolar epithelium. There are mitotic figures throughout the tumor. There are also many areas of necrosis. There are many widespread areas of peribronchial and perivascular organization distant from any tumor masses. There are small cancer emboli in the vessels leading to the infarcts in the right lung. Otherwise the right lung is conspicuously free from tumor.

Metastases: There are visceral metastases in the liver, suprarenals and lymph nodes. They resemble the primary tumor in structure. In some areas there is marked mucous secretion. The ovarian metastases have a striking resemblance to small bronchioles. There are bone metastases in the ribs and the skull. The tumor in the anterior fossa of the base of the skull extends into the orbits and compresses and invades the optic nerves. The structure is similar to that described elsewhere.

Summary.—The interesting points in the history were the striking family history of malignancy and the attack of influenza three months prior to the onset of symptoms. There were many areas of peribronchial and perivascular organization as further evidence of a preceding organizing inflammatory process. In the left lung there was a widespread invasion of the peribronchial and perivascular regions with many areas of extension into the surrounding pulmonary parenchyma. In the right lung the metastases were widespread and resembled the primary tumor. Histologically, there were great variations in the findings, and areas were seen within the primary nodule fitting perfectly the authoritative descriptions of carcinomas arising from the bronchial mucous membrane, the bronchial mucous glands, and the alveolar epithelium. The primary nodule was situated beneath the scar in the left upper lobe. It was just beyond the bifurcation of a small bronchus, in a position from which a bronchial or an alveolar tumor might arise.

CASE 5.—*Clinical History.*—F. G., a white male, aged 45 years, was admitted to the New Haven Hospital, March 2, 1920, complaining of a cold and pain in his right side. The family and personal history are unimportant. The present illness began Feb. 1, 1920, with sudden sharp pain on the right side of his chest following severe exertion. At this time he developed a cough with profuse expectoration of blood stained mucus. The pain in the chest and the cough have persisted. He has also had fever, night sweats and increasing dyspnea on exertion. He has lost 45 pounds in weight during the last month.

Physical Examination.—The physical examination on admission showed a markedly emaciated man. There were enlarged lymph nodes above the right clavicle. The right side of the thorax was somewhat flattened. At the right apex and down to the third rib in front, the percussion note was impaired and the expiratory sounds were prolonged. The signs did not suggest an active lesion at this time. The abdominal examination was negative. Ten days later the flattening of the right side had markedly increased; there was a conspicuous limitation of motion on this side and the supraclavicular lymph nodes had increased in size. The changes in the percussion note and the breath sounds were more pronounced; in front the retromanubrial dulness had distinctly increased toward the right; behind, there was dulness extending to the fourth dorsal spine, as well as over the entire base below the eighth dorsal spine. There was a slight kyphosis at the eighth and ninth dorsal vertebrae. A cervical lymph node was removed for diagnosis and the sections showed a metastatic carcinoma. A right sided pleural effusion developed later. Examinations of the sputum for tubercle bacilli were repeatedly negative. The pulmonary signs steadily increased, the fever, between 100 and 103 F., was continuous and there was increasing dyspnea and emaciation until death on June 28, 1920.

Clinical Diagnosis.—Primary carcinoma, probably arising in a bronchus with invasion of the lung and mediastinum and metastases to the cervical lymph nodes and spinal column.

Necropsy 375 (Performed by Dr. Robinson about three days after death).—*Anatomic Diagnosis.*—Carcinoma of the bronchus; invasion of the lung, pleura, mediastinum and pericardium; compression of the bronchi; chronic tubular bronchiectasis; metastases to the regional lymph nodes, liver, vertebrae, sternum and clavicle; fibrous pleurisy and pericarditis; emaciation; decubitus.

Protocol.—(Abstract.) The body is that of an emaciated white male, measuring 172 cm. in length and weighing 112 pounds. Rigor mortis is not present. The cervical lymph nodes are enlarged. The right side of the thorax is definitely flattened. There are decubitus ulcers over the fifth dorsal spine and the tip of the sacrum. The peritoneal surfaces are everywhere smooth and glistening and the abdominal organs are normally disposed. The liver edge extends 6 cm. below the costal margin in the right midclavicular line and there are numerous elevated nodules on the surface. There is a tumor mass.

filling the anterior mediastinum. The right pleural cavity is obliterated by extensive pleural adhesions. The left lung is entirely free from adhesions. The pericardial cavity is also obliterated by adhesions.

Lungs: After removal of the lungs, the mediastinal structures and the trachea en masse, a view of the tumor is obtained. There is a large yellowish-gray tumor filling the anterior mediastinum, surrounding the trachea, and continuing up to the lower border of the thyroid. There are extensive pleural adhesions over the entire right lung and there are numerous tumor nodules on the pleural surface. Numerous frontal sections through both lungs, the main bronchi, and the trachea reveal the distribution of the tumor. There is a large mass beneath the bifurcation of the trachea involving the hilic lymph nodes on both sides and compressing the main bronchi. There is also a large mass extending along the right side of the trachea with a smaller mass on the left. The parenchyma of the left lung shows no metastases. The right lung is extensively invaded by the tumor. The main bronchus to the right upper lobe communicates with a large cavity measuring about 5 cm. in diameter. The walls of the cavity are necrotic and the lumen is filled with a thick mass of necrotic cellular débris. There is a large mass, apparently the oldest portion of the tumor, completely surrounding this cavity, measuring about 5 cm. in its greatest diameter. This mass forms a wide band extending to the hilus and connecting with the mediastinal tumor.

In the less involved sections of the lung the usual picture is seen. There are bands of tumor encircling the bronchi and blood vessels (Fig. 13). These perivascular and peribronchial tumor masses become progressively larger as the hilum is approached. There are no definite nodules projecting into the lumina of the bronchi, although the mucous membrane of the lower portion of the trachea and both main bronchi is absent and the surface is rough and finely granular in appearance. The bronchioles of the lower lobe are dilated and contain a creamy purulent exudate. A section of the tumor is yellowish-gray in color and the extensive areas of necrosis give the surface a lobular appearance.

Microscopic Notes.—Lung: The sections of the right lung show a typical keratinizing squamous celled carcinoma (Fig. 14). There are numerous strands and solid nests of large polyhedral cells infiltrating the peribronchial area. These cell nests are irregular in size and shape. Some are apparently situated in the lymphatic vessels, others are surrounded by a dense fibrous stroma. In many areas epithelial pearls and areas of keratinization are seen. There are areas in which carcinoma cells are seen filling the alveoli and in a few places the tumor cells in adjacent alveoli are connected by extension through the alveolar walls. Mitotic figures are numerous. Carcinoma cells are also seen within the blood vessels.

The bronchial mucous membrane is absent in many cases. In some bronchi the normal mucosa is present and in other areas the epithelium is hyperplastic and forms many layers of somewhat irregularly arranged cells. There are widespread areas of necrosis throughout the lung. In these areas the tumor cells and normal structures of the lung appear in phantom outline only.

The left lung shows only an occasional small accumulation of cancer cells in the peribronchial area. There is a widespread thickening of the alveolar walls.

Metastases. There are gross metastatic nodules in the hilic lymph nodes and in the liver and microscopic metastases in the pericardium. In the lymph nodes there are many epithelial pearls and areas of keratinization. In the liver there are nodules of densely packed, large polyhedral cells without areas of keratinization. Mitotic figures are conspicuous.

Summary.—The widespread fibrous thickening of the alveolar walls and the metaplastic bronchial mucous membrane are evidences of a preceding inflammatory process. The right lung was extensively involved with widespread invasion of the peribronchial regions, as well as of the surrounding pulmonary parenchyma. There were only a few microscopic carcinomatous

nodules in the left lung. Presumably the primary site was in the region of the cavity in the right upper lobe. Histologically, the tumor was a typical squamous cell keratinizing carcinoma. The metastases resembled the primary tumor. There was no doubt concerning the primary bronchial character of this tumor, and it very probably arose in metaplastic bronchial mucous membrane.

DISCUSSION

Incidence.—The five cases reported in this paper have occurred in a consecutive series of 375 postmortem examinations among which there have been a total of twenty-nine carcinoma cases. Although the series is small, these figures, 1.38 per cent. of all necropsies and 17 per cent. of all carcinomas, are high in comparison with those usually given.

It may be noted, as regards sex, that three of the tumors were in males and two in females.

Clinical Characteristics.—The clinical characteristics may conveniently be discussed according to the four clinical groups outlined above, that is, (1) small solitary tumors producing no clinical symptoms; (2) tumors in which the dominant symptoms are produced by cerebral or other metastases; (3) those in which the patient is first seen in a moribund condition, and (4) those showing symptoms and signs or more or less extensive pulmonary involvement with or without metastases. No case of this series belongs to the first comparatively rare group. In group 2 there are Cases 1 and 4. In Case 1 the patient was unconscious when admitted to the hospital, and the history and physical examination were entirely dominated by cerebral symptoms. This case may also be placed in group 3. In Case 4 there were symptoms and signs of a malignant tumor with generalized metastases involving particularly the brain and the lungs. An excised lymph node showed an adenocarcinoma. A mass was palpated in the region of the right kidney and a clinical diagnosis of an adenocarcinoma arising in this region was made. In group 4, Cases 2, 3, and 5 are included. In Case 2 there was evidence of extensive pulmonary involvement, enlarged cervical lymph nodes, and a nodule on the third rib; however, the sudden death of the patient from pulmonary thrombosis on the day after admission prevented a thorough clinical study. In Case 3, there was evidence of an intrathoracic tumor with symptoms of pressure on the recurrent laryngeal nerve. The clinical diagnosis was an intrathoracic carcinoma. In Case 5, a clinical diagnosis of primary carcinoma of the bronchus was made. This diagnosis was based upon the increasing right sided intrathoracic signs during the patient's stay in the hospital with a simultaneous enlargement of the cervical lymph nodes, one of which was excised and showed a metastatic carcinoma.

In an analysis of the clinical aspects of bronchial tumors, Weller [12] emphasizes the value of bronchoscopic and radiographic examinations and the absence of fever and night sweats as important factors in

reaching a diagnosis. Bronchoscopic examinations of the five cases reported here were not made. It is probable that this method would have revealed the nodule in the lower portion of the trachea in Case 4 and the roughened and granular appearance of the lower portion of the trachea in Case 5. Such findings, however, would not have materially altered the diagnoses. Radiographic examinations showed the large mediastinal tumor in Case 4 and the progressive character of the pulmonary lesion in Case 5. Contrary to Weller's findings, however, fever was present in all five cases (the temperature ranging from 96 to 103 F.), and night sweats were present in one case.

In three of the five cases a clinical diagnosis of a malignant tumor was made. In two of these the diagnosis was established by examinations of excised lymph nodes. In the other two cases a diagnosis was not possible since there was no opportunity for proper study.

Metastases.—According to the extent of the metastases, carcinomas of the lung fall into three groups; (1) cases without metastases; (2) those with intrathoracic metastases only, and (3) those with generalized metastases. The cases reported in this paper fall into groups 2 and 3. Case 3 showed no metastases outside of the thoracic cavity. The remaining four cases showed widespread metastases.

As was stated above, a high percentage of lung carcinomas show generalized metastases. This may be explained by the close relation between lung tumors and the pulmonary circulation whereby tumor cells may be readily transported to the heart and into the general circulation. In favor of this suggestion the five cases reported here showed carcinoma cells within the pulmonary vessels, and, in Case 4, carcinoma cells are seen not only in the lumen, but also within the wall of a small vessel (Fig. 12).

Furthermore, all five cases show evidence of invasion and spread through the lymphatic channels, and four show evidence of extension through the air spaces. The extension of lung tumors through the air spaces is important as areas are seen not infrequently in which it is difficult to differentiate between tumor cells growing along the alveolar walls and regenerative changes in the alveolar epithelium. Areas showing such alveolar extension may be confusing and lead to an incorrect diagnosis of alveolar origin.

Four of the cases afforded the interesting and unique observation of cancer cells extending through the alveolar walls. In some areas (Fig. 4) this was quite striking and recalled the pictures of the fibrin bundles extending through the so-called pores of Cohn in a pneumonic lung.

Gross and Histologic Features.—Gross Features: The cases reported in this paper are rather advanced stages and show infiltrating tumors with very extensive involvement of one lung and the regional lymph

nodes. Four cases present the picture that is most frequently described in primary bronchial carcinomas. The only exception is Case 1, in which there were diffusely scattered peribronchial and perivascular tumor nodules, a picture possibly identical with the so-called miliary carcinosis of the older writers.

Histologic Features: The histologic findings in these cases are as follows: (1) cylindrical cells (Cases 3 and 4). Case 4 is a typical cylindrical cell tumor showing a marked variation in the picture presented, and Case 3 is a cylindrical cell tumor showing a uniform picture, with a perivascular arrangement of the cells; (2) polyhedral cells (Cases 1 and 2). These cases show a predominant polyhedral cell with areas in which the arrangement and form of the cells suggest the squamous variety. However, the absence of epithelial pearls, areas of keratinization or prickle cells is against this interpretation, and for the sake of exactness it seems advisable not to place tumors in the squamous cell group in which these findings are entirely absent; (3) squamous cells, Case 5 is a typical squamous cell tumor with epithelial pearls and areas of keratinization.

Histogenesis.—The question of histogenesis has absorbed the attention of many authors and it is unusual to find cases recorded in which a positive conclusion concerning the origin from the bronchial mucosa, the bronchial mucous glands, or the alveolar epithelium is not definitely stated. However, the criteria on which the exact site of origin is determined have been variously stated by different authors and this, in itself, is an indication of the difficulties of reaching a correct conclusion. There are a few cases of solitary papillomata arising in the wall of a bronchus or a tuberculous cavity in which the histogenesis is clear. There are other cases generally accepted as of undoubted alveolar and bronchial mucous gland origin, notably those of Langhans [4] and Kretschmar,[23] in which the diagnoses are probably correct. However, the great majority of cases are seen in an advanced stage and it is difficult or impossible to determine the histogenesis accurately. The points on which the diagnoses are made are not pathognomonic of alveolar and bronchial mucous gland tumors. The chief criterion on which conclusions concerning the histogenesis of lung tumors have been made is resemblance between the tumor and the normal structures. These resemblances are frequently striking and almost convincing, but the study of the present series of tumors shows, in one case (Case 3) at least, in a single tumor, areas resembling the authoritative descriptions of tumors arising from the bronchial lining epithelium, the bronchial mucous glands, and the alveolar epithelium. These findings are seen within the primary tumor which is situated near the bifurcation of a small peripheral bronchus, a site from which any type of tumor might arise.

It is also frequently stated that tumors arising in the bronchial mucous glands are largely situated in the bronchial wall producing a thickening of the wall and narrowing the lumen. But there is a serious fallacy in attributing much importance to this finding as one of the main lymphatic channels of the lung is situated in the bronchial wall and in the peribronchial area which constitutes, therefore, a natural line of growth for any malignant tumor of bronchial origin.

The bronchial lining epithelium and the bronchial mucous glands normally have mucus secreting cells and the presence of mucous secretion is not convincing evidence in favor of an origin from the mucous glands.

In alveolar tumors, it is also stated, that there are diffuse areas suggesting an organizing bronchopneumonia. It is very doubtful, if much, indeed, if any, significance can be attached to such a finding. Lung tumors are usually of widespread distribution and as has been stated above in four of the five cases reported, there is an extension into the pulmonary parenchyma, the cancer cells apparently growing along the thickened alveolar walls replacing the alveolar epithelium and filling the alveolar spaces. The alveolar epithelium, not infrequently assumes a cuboidal form and may be piled up in several layers so that it is sometimes difficult to determine whether a small group of cells represents regenerating alveolar epithelium or a portion of the neoplasm. These findings are present in many cases and may lead to the false interpretation of alveolar origin.

The difficulties of making an exact histogenetic diagnosis have been mentioned by others (Paessler,[7] Adler[9]), but to find, within a single tumor, areas resembling the generally accepted cases of all three varieties throws further doubt on the possibility of determining the exact origin in the large majority of carcinomas of the lung. The five cases in this series are all of bronchial origin, but it is difficult or impossible to determine the more minute histogenesis except in Case 5 (a keratinizing squamous cell tumor), which apparently arose in the bronchial mucosa.

Relation of Irritation to Neoplastic Growths.—The emphasis that many authors have placed on chronic irritation from inflammatory processes as an etiologic factor in the causation of lung tumors has been previously mentioned. That carcinomas may result from certain types of chronic irritation is now generally conceded, and this phase of the subject will not be entered on except to mention the well known tumors following roentgen-ray dermatitis, the kangri cancers, and the chimney sweep cancers. In addition to these instances of definite association between irritation and the production of cancer there are other instances suggestive of such a relationship as in pipe-smoking and cancer of the lip, and the papillomas of the bladder in anilin dye workers.

Although considerable evidence has accumulated in favor of a causal relationship between chronic irritation and cancer, much less attention has been paid to the possibility of a neoplastic change being induced by an acute inflammatory process.

The five primary bronchial carcinomas reported in this paper have occurred in a comparatively short time in a series of twenty-nine carcinoma cases among a total of 375 necropsies. Although the series is small, these figures (1.38 per cent. of all necropsies and 17 per cent. of all carcinoma cases) are strikingly high in comparison to those usually given. In these cases there is a preceding history of chronic inflammation of the respiratory tract in two cases, a definite history of influenza three months prior to the onset of the present illness in one case, and histologic evidence of preceding inflammatory processes, including hyperplasia and metaplasia of the bronchial lining epithelium and peribronchial perivascular areas of fibrosis, in all cases.

This association of pulmonary infection and lung tumors has been emphasized in studies of tumors in mice. Tyzzer [43] reported a series of eighty-three tumors occurring in seventy mice, of which 62 per cent. were primary in the lungs, and fifty-two of the 70 mice, or 74 per cent., had primary lung tumors. Slye [44] found that one-third of all tumors of mice were primary in the lungs. Both Tyzzer and Slye observed evidence of preceding inflammation in many cases, and concluded that these tumors arose in areas of inflammatory hyperplasia.

The possible origin of these tumors in areas of inflammatory hyperplasia is particularly interesting in connection with the recent epidemic of influenza. In this disease a striking picture of epithelial proliferation is seen. The trachea, bronchi, bronchioles, and alveoli frequently show evidence of active epithelial proliferation running parallel to a widespread organizing process. In most cases the proliferation consists in a replacement in a more or less normal manner of the epithelium destroyed by the inflammatory process. In some cases, however, irregular cell nests extend into the surrounding newly organized area, producing a picture histologically indistinguishable from that seen in an infiltrating malignant epithelial new growth (Fig. 15). In discussing these regenerative changes, Winternitz, Wason and McNamara,[45] in their report on the pathology of influenza as seen in the recent epidemic, suggested the probability of an increase in lung tumors on the basis of the epithelial overgrowth observed.

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43. Tyzzer, E. E.: A Series of Spontaneous Tumors in Mice, with Observations on the Influence of Heredity on the Frequency of Their Occurrence, J. M. Research **21**:479, 1909.

44. Slye, M.; Holmes, H. F., and Wells, H. C.: The Primary Spontaneous Tumors of the Lungs in Mice, J. M. Research **30**:417, 1914.

45. Winternitz, M. C.; Wason, I. M., and McNamara, F. P.: The Pathology of Influenza, Yale Press, 1920.

The difference in the atypical epithelial proliferation in influenza and the comparatively orderly repair after lobar pneumonia is marked. The difference may be due to several factors—the site of the injury, the character and degree of the injury, and its repetition during the course of the disease. These differences have an analogy in the experimental study (Winternitz, Smith and McNamara [46]) of epithelial regeneration after intrabronchial insufflation of hydrochloric acid in rabbits. The insufflation of a solution of hydrochloric acid causes necrosis of the tissue which varies with the amount and concentration of the acid used. With weak solutions the epithelium alone may be destroyed and it is quickly regenerated in a comparatively orderly manner. If the injury has destroyed the lining epithelium, the basement membrane, and a portion of the surrounding structures, the regeneration takes place in a very different manner and an interesting picture is produced. The normal repair consisting of a single layer of cells, is seen in those areas in which the basement membrane is intact, but when the regenerating epithelium reaches areas in which the necrosis has extended through the basement membrane, the epithelial cells pile up and penetrate the necrotic portions of the subjacent pulmonary parenchyma. Not only does the newly formed epithelium grow along the intact basement membrane and into the surrounding parenchyma in areas where the basement membrane is destroyed, but the proliferating cells extend over the dead epithelial membrane lying free in the lumen. Subsequently, this necroic tissue may become organized with the formation of definite polypoid structures. With more marked pulmonary injury in which the acid has destroyed wide areas of lung tissue, the proliferation is more marked. The newly formed epithelial cells apparently extend out along the scaffolding of the necrotic alveolar walls, and in some areas the irregularity of the epithelial proliferation within the newly organized areas of destroyed pulmonary parenchyma presents a histological picture resembling a malignant epithelial tumor. The reparative changes in lobar pneumonia are analogous to those following slight chemical injuries, such as after weak acid, whereas the epithelial regeneration following influenza is comparable to that which follows a severe injury such as is produced by stronger acid. The association of the different degree of regeneration with the destruction of the basement membrane is interesting and agrees with the observation of Haythorn, that true squamous cell metaplasia of bronchial epithelium is always associated with destruction of the membrana-propria.

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46. Winternitz, M. C.; Smith, G. H., and McNamara, F. P.: Epithelial Proliferation Following the Intrabronchial Insufflation of Acid, J. Exper. M. **32**: 205, 1920.

The ultimate fate of the exuberant epithelium produced by the intra-bronchial insufflation of hydrochloric acid in rabbits is not known, as only the earlier stages have been studied. It is probable that the epithelial proliferation both in influenza and in experimental acid insufflation, will undergo regressive changes in the majority of cases or else remain quiescent and appear as isolated epithelial structures in a dense scar. However, it is not improbable that in a small percentage of these cases the activity of the epithelium may develop into a true neoplastic process. It is quite conceivable, as suggested above, that the relatively high incidence of carcinoma of the lungs in this hospital during the past two years may be referable to postinfluenzal lesions even though the clinical history in a majority of cases was not definite as regards an antecedent infection.

CONCLUSIONS

1. Classification of carcinomas of the lungs, either on a basis of gross pathological or histological structure, is difficult and unsatisfactory. The majority of cases are seen in a late stage; and while there are morphologically several definite types, including mucus secreting adenocarcinomas, and prickle cell tumors, the majority of cases do not fall into well defined groups but present striking variations in structure in different parts of a single tumor which are especially confusing.

2. The exact origin of tumors of the lung from the bronchial mucosa, the bronchial mucous glands, or the alveolar epithelium, is in general impossible to determine with certainty, but gross and microscopic evidence point strongly to a bronchial origin for most of the tumors. All five of the cases herewith reported very certainly originated either in the bronchial mucosa itself or in its glands.

3. According to composite statistics compiled prior to 1917, carcinoma of the lungs was found in approximately 0.36 per cent. of necropsies and 1 per cent. of all carcinomas. During the past three years five cases have been found at the New Haven Hospital in 375 necropsies, or 1.38 per cent. of all necropsies, and 17 per cent. of carcinomas. Whether these figures indicate a real increase in the incidence of carcinoma of the lung is doubtful, but the observation is at least suggestive.

4. The lungs in fatal cases of influenza occurring in the recent epidemic showed very regularly severe damage to the bronchial and alveolar epithelium, often associated with striking and atypical epithelial proliferative changes resembling early carcinomas. Such lesions suggest the possibility of a causal relation between influenzal infection and the recent apparent increase in carcinoma of the lungs, indicated by the figures given above.

EXPERIMENTAL DIABETES INSIPIDUS*

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INTRODUCTION AND HISTORY

It has been known for a long time that tumors and other pathologic lesions in the region of the sella turcica are attended by far-reaching pathologic alterations in other parts of the body. For some time also it was a matter of dispute among clinicians as to whether the symptoms were due essentially to lesion of the pituitary gland or of the immediately adjacent base of the brain (Erdheim[1]). Recently this controversy has arisen anew in the contradictory articles of Leschke[2] and Marañón.[3]

In 1907 Paulesco[4] opened the way to a solution of the question by developing a method of operative approach to the region of the sella. By this method, perfected by Cushing and developed by him and his associates, operative procedures on the pituitary gland became relatively easy.

Cushing[5] was the first to note, after experimental lesions of the pituitary in dogs, the development of a syndrome identical with that known clinically as adiposogenital dystrophy. The syndrome in his experience followed most frequently division of the pituitary stalk, an observation recently confirmed by Bell.[6] The same dogs had a persistent polyuria. These results are usually attributed to deficiency of the secretion of the pituitary gland: the adiposogenital dystrophy to deficiency of the anterior lobe, the polyuria, to deficiency of the posterior lobe secretion. The latter opinion concerning the polyuria has been supported by the effects of subcutaneous injection of pituitrin and is widely accepted.

Shortly afterwards Aschner[7] operating by the buccal route on dogs, denied the possibility of producing adiposity in adult animals by removal of the gland. On the other hand, he reported, after hypophysectomy in young dogs, the production of adiposity, genital aplasia, high

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1. Erdheim: Sitzungsb. d. k. Akad. d. Wissensch., math. naturw. Cl., Wien., Abt. 3 **113**:537, 1904.
2. Leschke: Ztschr. f. klin. Med. **87**:201, 1919.
3. Marañón: Nuevas orientaciones sobre—de la Diabetes Insipida, 1920.
4. Paulesco: L'hypophyse du cerveau, 1907.
5. Cushing: The Pituitary Body, 1912.
6. Bell: The Pituitary, 1920.
7. Aschner: Arch. f. d. ges. Physiol. **146**:1, 1912.

adrenalin tolerance, and general underdevelopment, a syndrome identical with that known clinically as pituitary infantilism. These symptoms he ascribed to lack of the pituitary secretion. The occasional occurrence in adult animals of other symptoms noted by Cushing, such as cachexia, subnormal temperature, adiposity, genital atrophy and death, he thought to be due to gross lesion of the brain. This latter assumption was purely gratuitous as any one who has examined a brain after a temporal pituitary operation must realize, even when done by a much less skillful surgeon than Cushing.

Aschner was vigorously criticized by Biedl [8] for assuming such a totally unknown hypothetical nervous center as a cause for the symptoms. And there is an evident lack of coordination in Aschner's conclusions in that he attributed the genital atrophy in young animals to lack of pituitary secretion and the identical condition in adult animals to a lesion of the base of the brain! Indeed, at that time so little was known concerning the connections and functions of the part of the brain just above the pituitary, that the idea that a lesion in this region so small as to escape naked-eye examination could cause such widespread results as polyuria, genital atrophy, adiposity, cachexia, and even death must have seemed to any one absurd. But though at the outset confusion and contradiction existed in the physiology of the pituitary, it came to be generally accepted that adiposogenital dystrophy and polyuria were due to an hypophysial lesion.

Since that time, however, some experiments have been reported, acute and rough though they were, which seem to indicate that in the base of the brain just over the pituitary is a very important center, intimately connected with the entire visceral nervous system. Lesion or stimulation of this region, known to anatomists as the hypothalamus, is said to be followed by dilatation of the pupil (Karplus and Kreidl [9]), a disturbance of heat regulation (Isenschmidt and Krehl,[10] Ott,[11] Leschke,[2] Barbour [12]), glycosuria (Aschner [13]), polypnea (Garrelon and Langlois [14]) and many other symptoms.

The anatomic relations of the hypothalamus are still imperfectly understood, but it is known to be closely related to the olfactory and gustatory (Herrick [15]) systems, which are highly specialized parts of the visceral nervous system. There is also some evidence of

8. Biedl: Innere Sekretion, 1912.
9. Karplus and Kreidl: Arch. f. d. ges. Physiol. **129**:138, 1909.
10. Isenschmidt and Krehl: Arch. f. exper. Path. u. Pharmakol. **70**:109, 1913.
11. Ott: Fever, Its Thermotaxis and Metabolism, 1915.
12. Barbour: Physiological Reviews **1**:295, 1921.
13. Aschner: Berl. klin. Wchnschr. **53**:772, 1916.
14. Garrelon and Langlois: J. d. physiol. **15**:566, 1913.
15. Herrick: J. Comp. Neurol. **15**:375, 1905.

its connection with the general visceral system (Brugsch, Dresel and Lewy [16]).

Camus and Roussy [17] were the first to undertake to control systematically the physiology of the pituitary by puncturing the base of the brain. Already in 1913 they had reported to the Société de biologie that they were able to produce transitory polyuria by puncturing the hypothalamus of dogs through the sphenoid bone with a heated drill. In one dog a permanent polyuria and in addition adiposogenital dystrophy had resulted. However, no microscopic examination was reported and it was often evident on gross examination that a lesion of the pituitary also existed. Especially was this true in the more interesting of their dogs, the one with a permanent diabetes insipidus with testicular atrophy. The report stated that the lesion lay in front of the infundibulum. This was much dilated, and the pituitary itself weighed only 20 cg. They concluded that the polyuria was due to a lesion of the gray matter of the tuber cinereum in the region of the infundibulum. They were not affirmative about the adiposogenital syndrome.

From time to time since then they have reported further experiment,[18] and have shown conclusively that the polyuria does not depend on a lesion of the hypophysis by producing it in a dog from which the hypophysis had been previously removed. The removal of the hypophysis was followed by a transitory polyuria. More than a month later, after the polyuria had subsided, a second polyuria of equal intensity was produced by puncture of the tuber cinereum. Their conclusions have been supported by Houssay [19] without adding any new information. It is interesting, in view of the results given later in this paper, that he was unable to produce these symptoms in operating by the temporal route, probably because of unfamiliarity with the operative procedure.

Recently Camus and Roussy [20] in demonstrating two dogs with adiposogenital dystrophy to the Société de neurologie admitted that a lesion of the pituitary was probably present, although they brought strong arguments to show that it was not essential. Indeed in operating by their method it is difficult to avoid puncturing the pituitary, which lies directly under the hypothalamus.

Since it seemed difficult to arrive at a decision by this method with its almost necessary concomitant injury of the hypophysis, we

16. Brugsch, Dresel and Lewy: Ztschr. f. exper. Path. u. Therap. **21**:358, 1920.
17. Camus and Roussy: Compt. rend. soc. Biol. **75**:483, 1913.
18. Camus and Roussy: Endocrinology **4**:507, 1920; Compt. rend. soc. Biol. T. **83**:1578, 1920.
19. Houssay: Endocrinology **2**:94, 1918; Compt. rend. soc. Biol. **81**:381, 1918.
20. Camus and Roussy: Rev. neurol. **27**:1113, 1920.

determined to attack the hypothalamus by the temporal route, which allows an exposure of the entire region, with intent to study in detail the resulting polyuria. The lesion can be produced where desired, and the pituitary, being in plain view, carefully avoided. Needless to say, no trauma whatsoever is produced by the slight cerebral dislocation necessary for this exposure.

The present report is concerned with a series of such experiments, with especial reference to the resulting polyuria, leaving the discussion of the adiposogenital syndrome for a later communication.

METHODS

Dogs were used throughout our experiments. The technic of the temporal operation has been described in detail by Crowe, Cushing and Homans.[21] After the first few operations this procedure was modified somewhat to suit our purposes. The curved incision used by Bell [6] was found adequate. On the right side a subtemporal decompression was done as usual. On the left side we adopted practically the procedure of Sweet and Allen.[22]

> The superficial muscles are drawn down below the zygoma. A horizontal incision is then made through the periosteum along the middle of the zygoma for its entire length. The periosteum is stripped off the zygoma upward and downward. The zygoma is resected. From the middle of this horizontal incision another is made through the temporal muscle slanting upward and backward in the direction of the muscle fibers. In the upper part this latter incision is carried down to the skull. In the lower part the coronoid process of the mandible intervenes and must be removed before the incision can be extended downward. The temporal muscle is stripped from the skull and held to right and left with retractors. The bone is then trephined and the operation continued as usual. This procedure permits of a very low approach, direct access to the pituitary with a minimum of retraction of the brain and a perfect closure.
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> The pituitary region having been brought into view it is easy to recognize optic nerves, stalk, pituitary, internal carotid, etc., and to make lesions in any part of the hypothalamus at will. For making the lesion in the brain at first we used a right-angled knife which was slid between the pituitary and base of the brain, the point turned upward, thrust into the brain and then drawn to one side. After cutting the circle of Willis, however (Dog 12), it was discarded for a sharp right-angled probe. After the first three dogs also we contented ourselves with a much smaller lesion.

A few buccal operations were done following the technic described by Aschner,[7] and also a few punctures after the manner of Camus and Roussy by boring through the sphenoid with a dental drill, and puncturing the brain with a sharp probe.

The brains were removed as described by Crowe, Cushing and Homans after fixation in situ by carotid injection of formalin, with

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21. Crowe, Cushing and Homans: Johns Hopkins Hosp. Bull. **21**:127, 1910.
22. Sweet and Allen: Ann. Surg. **57**:485, 1913.

the exception of Nos. 10, 17 and 22. In these cases the body of the sphenoid was removed through the mouth as in a buccal operation and the dura carefully cut around the edge of the bony defect. The brains were then removed as before from above, the dura remaining attached to the entire hypothalamic region.

The hypothalamus was removed in one block, from the optic chiasm to the pons, with the pituitary attached. The block was embedded in celloidin, cut in 20 microns serial sections, and stained with van Giesen's mixture. In Dogs 7, 13, 15 and 16 the pituitaries were cleanly severed from the brain, embedded in paraffin and cut 6 microns in series for more careful study since in these cases there was some question of injury to the pituitary. In Dog 10, every fourth section of the brain was stained with thionin.

PROTOCOLS

The location of the lesion in each dog except the first two may be seen by referring to Plate 1.

Dogs 1 and 2.—Adult dogs: No. 1, partial anterior lobe removal, verified histologically. No. 2, posterior lobe removal, verified histologically. Neither dog had polyuria. At necropsy the remaining pituitary tissue normal histologically in each case. Base of brain not sectioned.

Dog 3.—Male, adult, 13.2 kg. Puncture by temporal procedure, November 3; previous average output 300 c.c. Polyuria second day. Maximum 1,500 c.c., November 12. Apathy, drowsiness, arched back, convulsions, hypothermia. Died in convulsion November 15.

Necropsy.—General examination negative; microscopically, lesion a puncture wound of the hypothalamus extending upward and forward to a depth of about 3 mm. Lesion directly back of the stalk of the hypophysis and slightly to the right of the midline. Hypophysis microscopically and macroscopically normal. Meninges normal. Testis showed acute atrophy of spermatogenic elements; rarely a spermatozoa or a spermatid is seen and they are absent in many tubules where the wall is composed of Sertoli cells and a few scattered spermatogonia; the spermatocytes show signs of degeneration in form of increased fat content. Suprarenal, pancreas, liver and kidney histologically normal.

Dog 4.—Male, adult, 25 kg. Temporal puncture November 18; previous average output 500 c.c. Polyuria the same day, 1,030 c.c. Coma, convulsions, death on the third day.

Necropsy.—Subcutaneous infection on left side. Meninges normal. General findings negative. Clean knife cut transversely across hypothalamus just back of stalk of hypophysis extending upward to a depth of 4 mm. Hypophysis intact. No signs of infection of the meninges.

Dog 5.—Male, adult, 11.8 kg. Temporal puncture November 30. Previous average output 700 c.c. Glycosuria first day. Polyuria the third day. Maximum 1,200 c.c. on sixth day. Apathy, drowsiness, arched back. Polyuria ceased the ninth day. Killed December 21.

Necropsy.—General findings negative. Microscopically two knife cuts, one into the mamillary bodies, the other just back of them extending upward about 3 mm. Hypophysis intact.

Dog 6.—Male, adult, 12 kg. Temporal puncture December 2. Previous average output 450 c.c. Polyuria the second day. Maximum 1,500 c.c. the third day. Polyuria ceased the seventh day. Aschner buccal operation,

December 18. Puncture in front of hypophysis. No polyuria, no symptoms except left hemianopsia. Killed January 31.

Necropsy.—General findings negative. Meninges normal. Two lesions, one a small puncture wound just behind and to the right of the hypophysis and extending to a depth of about 2 mm., the other a much deeper one extending from the optic chiasm to the thalamus. Pituitary intact.

Dog 7.—Male, puppy, 8 months, 13.4 kg. Average output 200 c.c. Aschner buccal operation March 1. Dura not opened. Curved dental probe slid around hypophysis and thrust into brain above it. No bleeding. Marked polypnea. Polyuria the first day 960 c.c., apparent recovery. Died the third day of meningitis.

Necropsy.—Meningitis. Puncture wound extending through the left mamillary body into midbrain. Pituitary infected.

Dog 9.—Male, adult, 15 kg. Temporal puncture, January 18. Previous average output 350 c.c. Polyuria the second day. Maximum the third day, 1,160 c.c. Ceased the fifth day. Killed February 2.

Necropsy.—General findings negative. Superficial lesion just back and to the right of the stalk. Hypophysis intact (Plate 2).

Dog 10.—Male, adult, 12.9 kg. Average output 450 c.c. Temporal puncture January 7. Enormous thirst. Polyuria the first day. Maximum the fifth day, 3,800 c.c. Permanent diabetes insipidus. Arched back and apathy the first days. Insidious and progressive drowsiness, obesity and genital atrophy. Kidneys denervated April 16. Transitory increase of polyuria and persistence later of the diabetes. Intramuscular injection of 4 c.c. epinephrin May 10, 9 a. m. No glycosuria. Killed May 10 in evening. Weight 20 kg.

Necropsy.—Enormous accumulation of fat generalized. Atrophy of external genitalia and testes. Thyroid not enlarged. Meninges normal. V-shaped lesion in hypothalamus just back of the stalk of the hypophysis. The posterior limb extended upward through the anterior margin of the mamillary bodies; the anterior slanted forward over the stalk to a depth of 3 mm. Anterior to the incision the cells of the tuber show chromatolytic changes. Behind the incision the nerve cells are normal. The entire pituitary was present. The posterior lobe had been detached from the infundibulum but was normal and its blood supply intact. The entire anterior lobe was present, its cells stained normally and its blood supply intact. Testes show an extensive atrophy of the spermatogenic elements. The spermatozoa are absent as well as most of the spermatids. Many pyknoses are seen in the spermatogonia. There is slight sclerosis of the walls of the tubules, very slight interstitial sclerosis, marked sclerosis of the albuginea, and extreme vascular sclerosis without endarteritis (Plate 3). The cells of the interstitial gland contain an abnormally large amount of fat which is collected in large globules. Suprarenal normal, lipoid content of cortex unaltered. Thyroid, parathyroid, pancreas, liver and kidney histologically normal.

Dog 12.—Male, adult, 12 kg. Temporal operation January 25. Operation abandoned without puncture because of profuse hemorrhage from circle of Willis. No polyuria. Marked sleepiness, contrasting with an excellent general state and which persisted until the animal was sacrificed. No choked disk. Killed February 15. Extensive pachymeningitis hemorrhagica interna.

Dog 13.—Male, adult, 13.4 kg. Average output 300 c.c. Temporal operation, February 7, abandoned because of hemorrhage from cavernous sinus. No symptoms. Removal of hypophysis by Aschner buccal procedure, February 21. Polyuria the first day, 1 000 c.c. Died February 23, with temperature of 109 F.

Necropsy.—General findings negative. Very little blood in subarachnoid space. No signs of infection. Pituitary entirely gone. Extensive lesion of the tuber cinereum which was not entirely destroyed but showed contusion and hemorrhage to a depth of 4 mm.

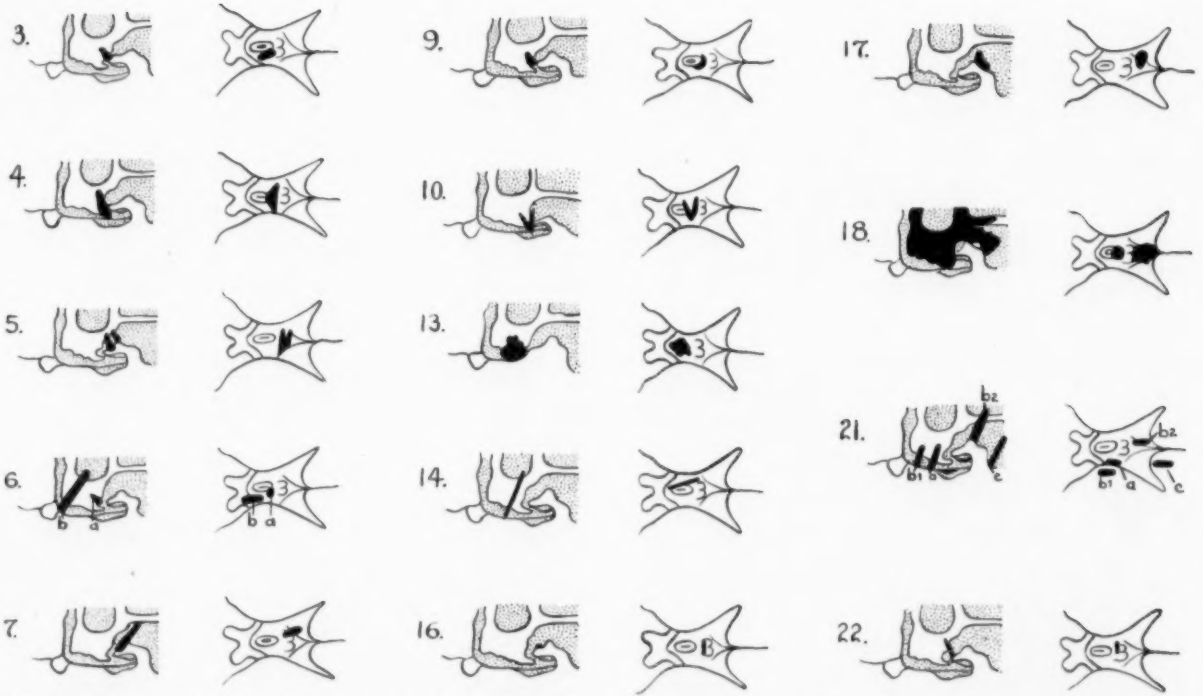

Plate 1.—Diagrams of lesions. The lesions are in black, projected on a median sagittal section and on the base of the brain.

Dog 14.—Male, adult, 19.6 kg. Chronic nephritis. Irregular polyuria, average 800 c.c. Puncture through sphenoid with a dental drill. Immediate polypnea which lasted twenty-four hours. Polyuria the third day. Maximum 2,300 c.c. Ceased the seventh day. Traces of glucose the third day. Killed April 11.

Necropsy.—Small contracted kidneys with capsule adherent. Minute puncture wound directly in front of the stalk of the hypophysis extending upward and backward to a depth of 15 mm. (Plate 2). Hypophysis intact. Kidney showed subacute nephritis.

Dog 15.—Male, adult, 10.7 kg. Temporal operation February 19. Strong trace of glucose first day. No polyuria. No other symptoms. Killed March 11.

Necropsy.—General findings negative. No lesion of hypothalamus could be found. Hypophysis intact.

Dog 16.—Male, adult, 13.6 kg. Average output 400 c.c. Temporal operation, February 26. Strong trace of glucose the first day. Polyuria the second day. Maximum 1,700 c.c. on same day. Ceased the eighth day. Killed March 15.

Necropsy.—General findings negative. Meninges normal. Superficial lesion at anterior border of mamillary bodies. Hypophysis intact.

Dog 17.—Male, adult, 10 kg. Temporal puncture March 29. Immediate polypnea. No polyuria. Died the first day.

Necropsy.—Considerable contusion of left temporal lobe. Lesion in left cerebral peduncle. Hypophysis intact.

Dog 18.—Female, adult, 10 kg. Temporal operation, April 5. Slight polyuria. Strong glycosuria. Died April 6 in coma.

Necropsy.—Intraventricular hemorrhage.

Dog 21.—Male, adult, 12 kg. Transsphenoidal puncture (a, Plate 1) April 23. No polyuria. Marked glycosuria. April 26, two similar punctures (b_1 b_2, Plate 1). Marked polypnea. No polyuria. Slight glycosuria. May 4, one similar puncture further back (c, Plate 1). No polyuria. Marked glycosuria. Killed May 10.

Necropsy.—Meninges normal. Four puncture wounds of the brain were found, only one of which (a) struck the optopeduncular region and was far lateral to the midline. One of the other three punctures struck the hypophysis producing a hemorrhage into the interlobar cleft.

Dog 22.—Male, young adult, 10 kg. Average output 400 c.c. Temporal puncture April 29. Polyuria the second day which did not subside, maintaining an average of 1,100 c.c. Kidneys denervated May 15, weight 15.2 kg. Subcutaneous infection, very ill. When the infection subsided the polyuria reappeared. May 25, weight 11 kg., general condition improving rapidly. June 5 injection of 4 c.c. epinephrin intramuscularly. No glycosuria. Killed June 10, weight 13.2 kg.

Necropsy.—Moderate generalized deposit of fat. Evidence of previous extensive intramuscular infection of lumbar region. Meninges normal. Lesion in hypothalamus at anterior border of the mamillary bodies. Hypophysis intact. Testis showed acute atrophy; spermatozoa almost completely absent, spermatids absent in many tubules, the remaining ones with increased fat content, swollen and degenerating. Increased amount of fat in the interstitial cells also. Kidney, suprarenal, thyroid, pancreas and parathyroid histologically normal.

Dog 23.—Female, adult, weight 14.6 kg. Average output 450 c.c., sp. gr. 1.026. June 1, kidneys denervated. Polyuria reaching a maximum of 900 c.c. June 3, output 760 c.c. June 4, temporal puncture, intake 1,800 c.c., output 600 c.c. June 5, apathetic. June 6, still apathetic; intake, 1,525 c.c., output, 997 c.c. June 7, cachectic, apathetic, with head drooping, arched back, profuse thick salivation, slow pulse and repeated typical epileptic attacks. June 8, some-

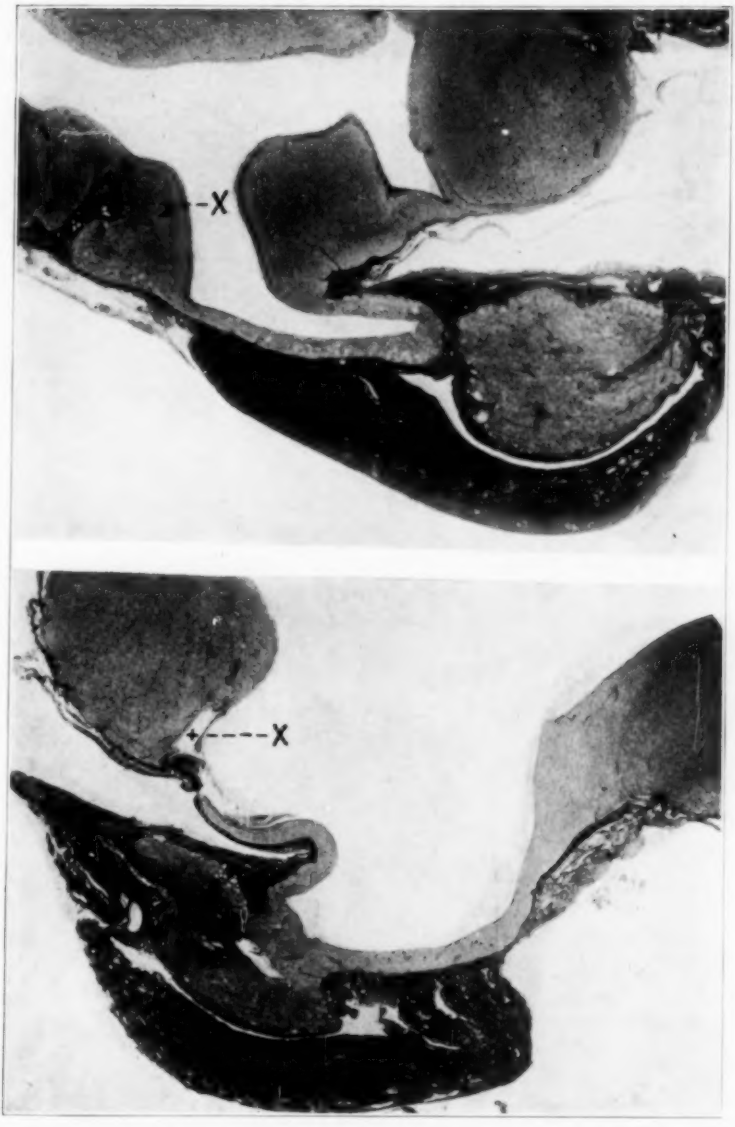

Plate 2.—Photomicrographs of approximately median sagittal sections of hypophysis and hypothalamus, × 14. The sections are reversed. Lesions shown at ×. Dog 14 above; Dog 9 below.

what improved, fewer attacks. June 10, much improved, injection of 4 c.c. epinephrin intramuscularly gave no glycosuria. June 11, much improved, intake 800 c.c., output 850 c.c., sp. gr. 1.018. Found dead in the morning of June 20.

STUDY OF THE SYMPTOMS

As an immediate result of the puncture we noted a sudden change in the respiratory rate which in one dog became a true polypnea lasting for twenty-four hours without other symptoms. In two cases also the animal gave a peculiar cry at the moment of puncture, both being nevertheless deeply narcotized at the time. We never observed any change in the rectal temperature within the first four hours.

1. *The Glycosuria.*—This was noted in six cases and had the characteristics of Claude Bernard's puncture glycosuria, the exact mechanism of which is still unknown. Stewart and Rogoff,[23] confirming others, have shown recently that it may be produced as well in animals whose adrenals have been removed. We made no attempt to determine the exact mechanism of its production in our animals.

In four of these dogs there was also a polyuria and it is interesting to note that in Dog 14, who had a chronic nephritis with marked retention of urea (nonprotein nitrogen 100), the trace of glucose appeared only on the third day along with the polyuria. It may be seen from the sketches (Plate 1, *5, 14, 16, 18*) that in each case the hypothalamus was involved in some way.

Two dogs (15 and 21) had glycosuria without polyuria. Dog 21 was punctured three times by the buccal route and each time had glycosuria. The lesions in this animal were all in the outskirts of the hypothalamic region and in Dog 15 no lesion could be found. It seems that the glycosuria does not depend upon so localized a region as the polyuria, and its production is known to depend very greatly on the nutritional state of the animal.

2. *Hyperthermia.*—One dog (No. 13) following ablation of the pituitary by the buccal route, had a temperature of 109 F. the second day, and died. The lesion in this dog who had also polyuria but no glycosuria affected extensively the tuber cinereum.

It has been shown by Ott, Isenschmidt and Krehl and others that the hypothalamus is the most important thermic center in mammals: thermic regulation and the possibility of inducing fever is abolished after section of the brain stem just behind it. Puncture of this region is followed in the rabbit (Ott [11]) by an immediate and extreme hyperthermia. The same hyperthermia, usually fatal, may follow operations on the pituitary region in man. That we did not observe it more frequently in our experiments is probably due to the small size of the lesion.

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23. Stewart and Rogoff: Am. J. Physiol. **46**:90, 1918.

Plate 3.—Photomicrographs of sections from the testis of Dog 10. × 70. The upper is stained with scarlet red; the lower with hematoxylin and eosin.

3. *Polyuria.*—In order to study the polyuria the dogs, kept in metabolism cages, were given free water supply and daily 1½ pounds of carefully weighed lean meat. The intake of water, output of urine, and the freezing point (Δ), specific gravity and total chlorids of the urine were charted. The presence of glucose and acetone in the urine was tested for before and after operation.

The daily output of urine on this regime in these animals, all adult, middle-sized dogs, varied from 200 to 500 c.c., but was very regular for each dog. Much more constant than the output were the freezing point and specific gravity. The freezing point varied between —3 and —4 in the different dogs, but each dog had a characteristic

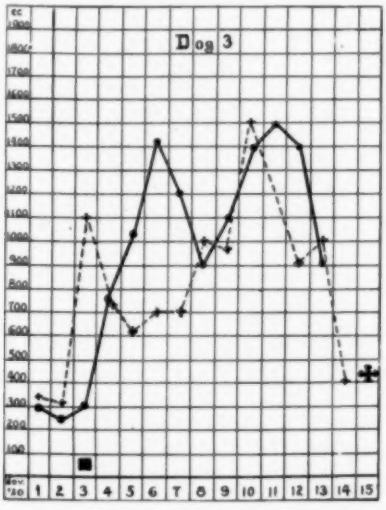

Fig. 1 +----+ Intake; ●—● Output; ■ Operation.

freezing point of an amazing constancy, fluctuating only two or three tenths of a degree. This is due to the fact that the dog eliminates urea to the maximal concentration (Ambard). After a few days of this regime poor in chlorids, the dog eliminates a minimal quantity of chlorids, from 0.8 to 1 gm., in twenty-four hours. They consist partially of potassium chlorid but for the sake of simplicity are evaluated in sodium chlorid. As has already been said, the dogs recovered completely within two hours after the operation. Most of them drank the day of operation and all, except the comatose ones and those operated by the buccal route, ate their entire ration the following day. Twelve of the fifteen punctured dogs had a polyuria.

Three dogs which were punctured had no polyuria (Nos. 15, 17 and 21). In Dog 15 no lesion could be found; in Dog 17 the only

lesion was in the midbrain and in Dog 21 the lesions were all around the edge of the optopeduncular region. Besides Dog 12, submitted to the same operation but not punctured because of a profuse hemorrhage from the circle of Willis, had no polyuria.

The polyuria began for five dogs the first day, for six the second day and for one the third day. This last dog had a chronic nephritis with retention. Though there was apparently long latency of the effect of the puncture on the regulation of water, in three cases where the polyuria did not appear until the second day there was already on the first day a considerable increase in the intake of water as compared

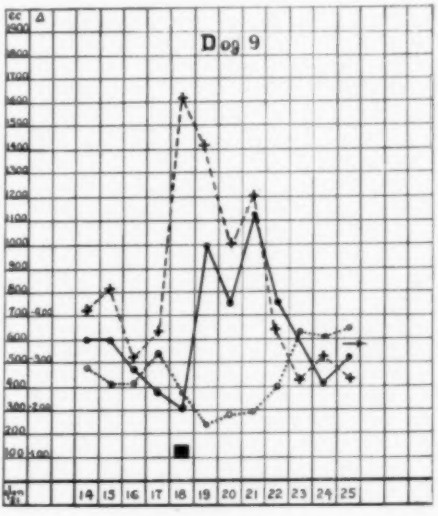

*Fig. 2. +---+ Intake; ●—● Output; o····o Δ; ■ Operation.

with the preceding days (Fig. 1, 2 and 3). Furthermore, e. g. in Dog 10, there was great disproportion between the intake and output on the days immediately following the operation, on the first day an intake of 2,500 c.c., and an output of 900 c.c., on the second, an intake of 3,600 c.c. and an output of 2,400 c.c. (Fig. 3). The same disproportion may be seen in Figure 2. This extreme discrepancy does not last more than two or three days. Soon an adjustment takes place, sometimes even the reverse discrepancy existing for a short time (Fig. 2). Whatever may be the cause of this early difference, the fact seems to be very important: it shows that polydipsia may precede the polyuria and is not simply consecutive to it.

Camus and Roussy do not mention this fact and their published curves do not show it. We have noticed that the dogs operated on by the buccal route did not drink the first day, which may explain their failure to observe this phenomenon. But these authors did remark various discrepancies between the intake and output later in the polyuria and employed the designation "trouble with the regulation of water" and they insist on the fact that the polydipsia, which they think nevertheless to be consecutive to the polyuria, is enormous, inordinate and seems at times to be out of proportion to the needs of the organism.

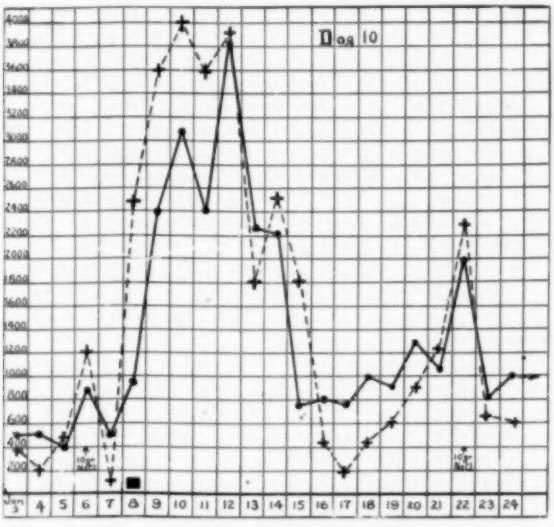

Fig. 3. +----+ Intake; ●—● Output; ■ Operation.

On the other hand, it is well known that the polyuria may appear (e. g. in comatose animals) and persist without any intake of water. We shall discuss later the significance of these facts.

In all but three dogs the polyuria lasted only from six to ten days and attained its maximum of from 1,000 to 3,000 c.c. on the third or fourth day as in the experience of Cushing [24] and of Camus and Roussy.

In the ten dogs with a polyuria in which a clean-cut lesion was found it was always located in the hypothalamus just back of the stalk of the pituitary, except in Dog 14 where it was just in front. Of the remaining two, one (No. 13) had an extensive lesion of the tuber and the other (No. 18) a hemorrhage into the third ventricle

24. Cushing: Boston M. & S. J. **168**:901, 1913.

with considerable trauma to hypothalamus and midbrain. It should be remembered that in the three dogs who were punctured but had no polyuria, no lesion of the hypothalamus was found but various lesions all around this region (including in Dog 21 the pituitary). Thus both the positive and negative results point to the same conclusion, namely, that the polyuria depends on a very small area just above the stalk of the pituitary known usually as the tuber cinereum.

4. *Permanent Polyuria.*—In three dogs the polyuria was permanent and had, as we shall see, all the characteristics of diabetes insipidus in man. These dogs presented other interesting symptoms: No. 3

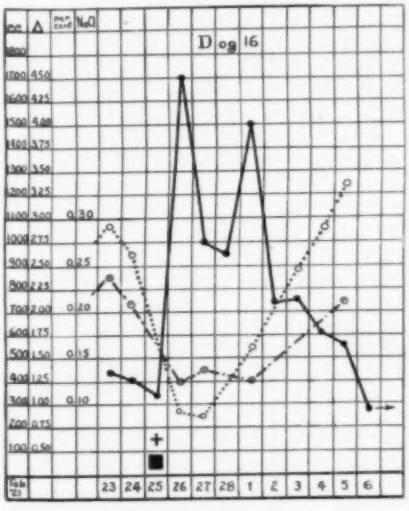

Fig. 4. ⊙---⊙ NaCl per cent; ●—● Output; o···o Δ; ■ Operation; + Sugar.

having progressive cachexia, hypothermia, and convulsions; Nos. 10 and 22 had typical adiposogenital syndrome. Such an association of symptoms is not a coincidence but is well explained by the lesions because in these dogs the lesion in the tuber was a more important one, although macroscopically very small. Those dogs having a still more extensive lesion of the tuber died very quickly as will be seen later.

In these polyurias the fall of the Δ, in other words, the total molecular concentration, was always more marked than the fall of the concentration of the chlorids (Table 1). The consequence was that the dogs during the days of excessive polyuria lost an appreciable quantity of chlorids, as much as 3 gm. in twenty-four hours. This

dissociation between the concentration of urea and other nonthreshold substances, and the concentration of chlorids is a banal one, as Cushny points out being found in all polyurias. It is explained in the modern theory of urinary secretion by impairment of the reabsorption of chlorids due to increased speed of flow in the tubules. In animals like the rabbit where there are other reasons for supposing a less developed power of reabsorption, any polyuria is accompanied by a marked increase in the percentage of chlorids in the urine (Cushny). After the polyuria had ceased it could be shown in three dogs that there was still a trouble of the regulation of water by the excessive polyuria provoked by the ingestion of chlorids.

TABLE 1.—Dog 10

Date	Urine 24 Hours	Δ	NaCl, per Cent.	Total NaCl	
1/ 3/21	500	—3.70	0.20	1.00	
1/ 4/21	580	—3.40	0.18	1.04	
1/ 5/21	425	—3.90	0.23	1.035	
1/ 6/21	900	—3.60	0.92	8.800	10 gr. NaCl
1/ 7/21	565	—2.95	0.46	2.56	
1/ 8/21	940	—0.45	0.18	1.69	Operation
1/ 9/21	2,400	—0.55	0.10	2.40	
1/10/21	3,040	—0.95	0.11	3.344	
1/11/21	2,150	—0.75	0.082	1.76	
1/12/21	3,800	—0.95	0.052	1.976	
1/13/21	2,240	—1.40	0.09	2.016	
1/14/21	2,180	.....	0.057	1.24	
1/15/21	670	—3.60	0.111	0.737	

Dog 10 after a week of extreme polyuria (as much as 3,800 c.c.) presented during four months, until sacrificed, a permanent and very regular polyuria. Dog 22 had also a permanent polyuria which we followed during more than a month. Previous to his puncture the daily output of Dog 10 was 470 c.c. with a Δ oscillating closely around —3.7. After the puncture the output was from 900 to 1,400 c.c. of a very pale urine and an average Δ of —2.2 Never was the previous Δ reached spontaneously. The constancy of this new concentration was such that the animal seemed to have adopted a new osmotic regulation and was in marked contrast to that observed in two nephritic dogs with polyuria which we had opportunity to observe. This constancy was very favorable for a systematic study, our aim being to verify that this polyuria had the characteristics of clinical diabetes insipidus. The same constancy was also present in Dog 22.

(a) *Influence of Deprivation of Food.*—No appreciable influence was observed.

(b) *Influence of Deprivation of Water.*—Dog 10 was restricted to 200 c.c. of water daily for two or three days. The output diminished only after the second day and then but slightly. The Δ reached

the neighborhood of —3. In one experiment there was an output of 1,000 c.c. on the third day of thirst, and the animal had lost at least 2,000 c.c. water. The blood, which was examined for us by Dr. Hilding Berglund before and at the end of the experiment, showed no evidence of concentration or retention.

(c) *Effect of Pituitary Extract.*—The effect of subcutaneous injection of pituitary extract was very interesting because Camus and Roussy state that it has no effect on the permanent polyuria which they produced in their dogs. The variations which they observed in the output after pituitary extract injections were of the same order

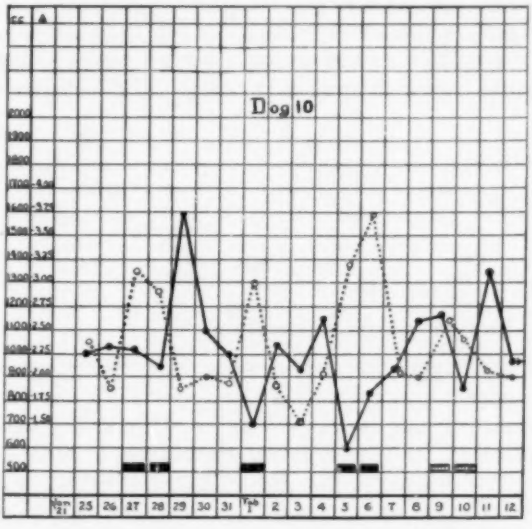

Fig. 5. Showing the action of Pituitary Extract and of reduction of the intake. ●—● Output: o···o Δ; ▬ 2 cc. Pituitary Extract in four injections ▬ Intake reduced to 200 cc.

as the daily variations. The failure to discover such an effect was probably due to the fact that they did not employ repeated small doses nor observe the Δ or specific gravity.

The effect of subcutaneous injection of pituitary extract (Parke, Davis & Co. pituitrin, and Lederle) was constant and definite, but much more apparent in the Δ than in the output (Fig. 5, Dog 10); it was the same in Dog 22. But the action, if we consider the dose employed and the necessity of repeated injections, is certainly less marked than in the average case of diabetes insipidus in man. Pituitrin had no definite action on the polyuria of two nephritic dogs.

(d) *Ingestion of Sodium Chlorid.*—The addition of an excess of sodium chlorid to the diet always produced a considerable increase of the polyuria. Normal dogs, living on a diet poor in chlorids, when given 10 gm. sodium chlorid with their meat consume it with avidity, have only a slight polyuria or none at all, and eliminate the first day from 6 to 8 gm. of the salt to a concentration of from 0.9 to 1 gm. per cent. This seems to be the maximal ability of the normal kidney to concentrate sodium chlorid as we have seen it in giving from 20 to 30 gm. The excess of sodium chlorid is eliminated in two, three or even four days.

Table 1 shows the effect of ingesting 10 gm. of sodium chlorid on Dog 10 before the puncture polyuria. Quite different was the result on the fourteenth day of polyuria (Table 2), when the output rose from 1,050 to 1,970 c.c. The concentration reached only 0.6, but 12 gm. chlorid were eliminated the first day and the elimination ceased

TABLE 2.—Dog 10

Date	Urine 24 Hours	Δ	NaCl, per Cent.	Total NaCl	
1/20/21	1,300	−2.35	0.13	1.69	
1/21/21	1,050	−2.10	0.155	1.62	
1/22/21	1,970	−1.4	**0.60**	**12.02**	10 gr. NaCl
1/23/21	780	−2.50	0.25	1.95	
1/24/21	700	−2.60	0.15	1.05	
1/25/21	1,000	−2.4	0.12	1.20	

the same day. This fact seems to us very interesting in view of the long prevailing doctrine that the polyuria of diabetes insipidus is a compensatory one due to the inability of the kidney to concentrate and the necessity for it to eliminate more water in order to perform its function of excretion (E. Meyer [25] and others). It is difficult to conceive that a reaction against a supposed defect could have a better final result than the normal kidney is able to attain. We have found curves showing the same acceleration of the excretion of sodium chlorid in diabetes insipidus of man in the papers of E. Meyer and of Kennaway and Mottram [26] given by these authors to show the inability of the kidney to concentrate!

The test was repeated twice on Dog 10 with the same result, namely the rapid elimination of the entire amount at a low concentration (from 0.33 to 0.45) with a marked increase of the polyuria. But it was possible to prove that the kidneys were perfectly able to concentrate normally the sodium chlorid by giving the salt on the second day of an experiment of thirst. Then the normal maximal

25. Meyer: Deutsch. Arch. f. klin. Med. **83**:1, 1905; Deutsch. Klin. **13**:282, 1911.

26. Kennaway and Mottram: Quart. J. Med. **12**:225, 1918-1919.

concentration of 1 gm. per cent. was reached and a Δ higher than before the operation (Table 3). A similar result was obtained where salt was given and pituitary extract injections with free water intake. The results with Dog 22 were entirely similar.

The polyuric action of chlorids is characteristic of diabetes insipidus (Oehme [27]). Our nephritic dogs did not show it. Therefore, it is interesting that we found the same excessive polyuria and quicker elimination of sodium chlorid not only during the polyuria but, by employing larger doses, after an apparent return to normal in dogs having a transitory polyuria. Dogs 5 and 6 a week after the cessation of their polyuria were given together with two normal dogs 30 gm. sodium chlorid. They had the first day a polyuria of 1,900 c.c., whereas the normal dogs passed only 1,000 and 1,200 c.c., and the elimination of the salt was much quicker. Dog 5 already after

TABLE 3.—Dog 10

Date	Urine 24 Hours	Δ	NaCl, per Cent.	Total NaCl	
2/14/21	850	−2.1	0.130	1.105	
2/15/21	950	−2.3	0.130	1.235	
2/16/21	1,580	−1.90	0.45	7.110	10 gr. NaCl
2/17/21	1,000	−2.4	0.224	2.240	
2/18/21	925	−2.5	0.215	1.988	
2/19/21	565	−2.9	0.200	1.130	200 c.c. H_2O
2/20/21	750	−4.05	1.097	8.227	200 c.c. H_2O, 10 gr. NaCl
2/21/21	1,300	−2.15	0.205	2.665	
2/22/21	1,000	−2.4	0.198	1.980	
2/23/21	1,020	−2.25	0.119	1.213	

the first day eliminated his normal chlorid. Other salts than chlorid, other crystalloids, and the purine derivatives have little or no effect on the polyuria of diabetes insipidus (Oehme). We have verified this statement in our dogs for theobromine.

(e) *The Effect of Fever.*—Fever was not provoked experimentally but Dog 10 had a slight attack lasting some days following an injection abscess. During this time the polyuria was greatly diminished and the concentration of the urine increased in spite of the fact that he did not eat his entire ration.

The results of all these tests justify the conclusion that the persistent polyuria provoked in this manner has all the characteristics of diabetes insipidus in man and is therefore a true experimental diabetes insipidus.

(f) *Effect of Denervation of the Kidneys.*—This was a procedure of great interest because, so far as we know, it has never been done either in clinical or experimental diabetes insipidus. The denervation

27. Oehme and Oehme: Deutsch. Arch. f. klin. Med. **127**:261, 1918.

was performed on Dog 10 on the ninety-eighth day of his diabetes by Dr. William Quinby whose experience with the procedure is well known.[28] All the nerves accompanying the renal vessels on both sides were destroyed and the surfaces of the vessels as far as possible decorticated. At this period, the polyuria, although constant, averaged only 750 c.c. with a Δ of —2.3 as against 470 c.c. with a Δ of —3.7 before the puncture.

The denervation was immediately followed by the polyuria which usually ensues. The maximal denervation polyuria observed by Dr. Quinby in his experiments on normal dogs was 1,000 c.c., an exceptional amount. Clearly Dog 10, who passed regularly 1,300 c.c. during eight days following denervation had two superimposed polyurias, one due to diabetes insipidus and the other to vasomotor disturbance produced by the denervation.

When the vasomotor polyuria had subsided after the usual delay the puncture polyuria continued until the animal was sacrificed, with the same characteristics. The average output was 850 c.c.; the Δ and specific gravity remained low; the effects of pituitary extract and sodium chlorid ingestion were unaltered, and the kidney showed the same ability to concentrate under the influence of pituitrin or restriction of water. A phenolsulphonephthalein test was done May 8, more than 75 per cent. being excreted in two hours and ten minutes. In the experience of Dr. Quinby this number is normal for dogs.

In Dog 22 the kidneys were denervated on the seventeenth day of his polyuria but owing to operative infection the immediate effect could not be observed. The slight fever he had accounts probably for the reduction of his polyuria and the rise of the Δ of his urine, which did not reach the level prevailing before puncture. As soon as the fever disappeared, the polyuria reappeared with exactly the same characteristics as before—the same Δ of —2.0 as against —3.4 before the puncture and the same ability to concentrate under the influence of pituitrin and restriction of fluids.

In Dog 23 a puncture polyuria was produced after the kidneys had been denervated.

We come thus to the important conclusion that the experimental diabetes insipidus is not suppressed by denervation of the kidneys and that the vasomotor polyuria following denervation may be superimposed on the diabetic polyuria.

(4) *Coma, Convulsions and Cachexia.*—Dog 4 died on the second day in a state characterized by coma and convulsive seizures. Dog 3 after an apparent recovery in which he was dull but ate normally

28. Quinby: Am. J. Physiol. **42**:592, 1916; J. Exper. M. **23**:535, 1916.

fell into a progressive cachexia with hypothermia and died in convulsions. It is true that Dog 4 had signs of infection in his left temporal region but this could not possibly be the cause of the immediate coma. No other finding could account for this clinical picture than the lesion of the hypothalamus just back of the pituitary stalk. In both the integrity of the pituitary was verified histologically beyond question.

Three other Dogs, 5, 23 and to a certain extent 10, in the days immediately following the operation showed the syndrome so well described by Cushing and called by him cachexia hypophyseopriva: head drooping, back arched and apathy. All these animals had polyuria, one glycosuria and one later developed the adiposogenital syndrome.

5. *The Adiposogenital Syndrome.*—In Dog 3 there was an acute testicular atrophy. The spermatozoa and spermatids were almost completely absent with degenerative changes in the other cells. It is probable that this dog would have developed the adiposogenital syndrome if he had lived.

The entire syndrome developed insidiously in Dog 10. After a slight apathy for a few days he seemed perfectly normal except for his polyuria. Then he began gradually to gain weight and grow apathetic and sleepy. He gained 8 kg. in three months. His testes and penis atrophied and he showed a complete indifference in the presence of a bitch in heat. The glucose tolerance could not be tested because he invariably vomited the sugar but intramuscular injection of 4 c.c. of adrenalin did not provoke a glycosuria. His hair which had been very rough became smooth and thin. He was also irresponsive to painful stimuli.

Dog 22 also had a testicular atrophy and gained considerable weight, most of which he lost, however, because of an acute infection, before it was necessary to sacrifice him.

DISCUSSION OF RESULTS

Perhaps the facts we have observed will throw some light on the pathogeny, still so obscure, of diabetes insipidus. We confirm the findings of Aschner, Camus and Roussy, and Houssay in showing that the polyuria is not due to injury of the pituitary gland but may be provoked with certainty by a lesion even extremely minute in the parainfundibular region of the hypothalamus. In most cases after such a lesion the polyuria is a transitory phenomenon but may be a permanent one which has all the characteristics of the diabetes insipidus observed clinically. In such cases there are also disturbances of metabolism and sexuality.

Is it possible to correlate this polyuria with those much more transitory ones induced in acute experiments by punctures or electrical stimu-

lation in various parts of the nervous system, e. g., the gyrus sigmoideus (Bechterew), the cerebellar vermis (Eckhard [29]), or the fourth ventricle (Eckhard,[29] Finkelnburg, Jungmann and Meyer [30])? We doubt it very much. These polyurias are immediate, small and very transitory. They are probably vasomotor phenomena, for at least that induced by puncture in the floor of the fourth ventricle cannot be produced after section of the splanchnic nerves (Eckhard [29]). On the contrary, we have seen that denervation of the kidneys in dogs with experimental diabetes insipidus, not only does not check their puncture polyuria but superimposes another on it. If we exclude the old experiments of Kahler which have been contested (cauterization of the fourth ventricle with silver nitrate), there is no evidence that a permanent polyuria can be obtained by lesion in these places. We may suppose, therefore, that the polyuria provoked by puncture of the hypothalamus is unique.

The first question which arises in interpreting the results of any experimental lesion of the nervous system is: are the effects noted due to an excitation or a destruction? The short duration of most of these polyurias suggests the former possibility in our experiments. But there are all transitions between the temporary and permanent polyurias as is also the case with clinical diabetes insipidus. Furthermore, study of the lesions shows that the location of the lesion is the essential factor. When the lesion is on the border of the necessary center or is extremely minute the polyuria is transitory. It would seem that destruction of the proper cells is necessary to a permanent polyuria. Besides in these cases there were other symptoms (cachexia, adiposity, genital atrophy) which are difficult to explain by an excitation. Of course, so far as the polyuria is concerned, the destruction of a nerve center may suppress an inhibition and so act ultimately as an excitation.

The second question which arises is: are the effects produced by direct nervous activity or through the mediation of some organ? We have seen that most probably the kidney is not involved. But we must consider one hypothesis both because of its historical interest and because of the seduction it offers to the mind, namely, the hypothesis of the pituitary origin of diabetes insipidus.

From the posterior lobe of the pituitary gland may be extracted a substance which has the remarkable property of being able to reduce all polyurias and especially that of diabetes insipidus. Although pituitary extract has a transitory diuretic effect, which was the first known, its ultimate action is a long lasting oliguria particularly apparent when these is a polyuria. Here is more than necessary to offer explanation of diabetes insipidus and in fact it has been attributed both to excessive

29 Eckhard: Ztschr. f. Biol. **44**: 1903.
30. Jungmann and Meyer: Arch. f. exper. Path. u. Pharmakol. **73**:49, 1913.

secretion of the diuretic pituitary extract by the posterior lobe (Schäfer) and to lack of the oliguric pituitary extract (most clinicans).

The first explanation can be rejected immediately because the diuretic effect of pituitary extract is transitory, and inconstant, being already absent on the second injection (tachyphylaxy). The second explanation requires more attention. Pituitary extract even when injected slowly has in the normal animal a definite inhibitory action on the diuresis. Oehme and Oehme, after careful study, concluded that it acts directly on the kidney cells (or perhaps on the ultimate ganglia) since its effect is not influenced by denervation of the kidneys and that it probably acts by storage in the cell and not by fall of concentration. The effect far outlasts the vasomotor one. Can it then be supposed that diabetes insipidus is due to a defect in the secretion of the posterior lobe caused by a lesion of its regulatory center in the hypothalamus? We think not. The posterior lobe may be completely removed without producing a polyuria, and the same polyuria may be produced after the hypophysis has been previously removed (Camus and Roussy [18]).

Pituitrin has never been proved to be discharged into the circulation. The anatomic evidence, moreover, is entirely against the supposition that the posterior lobe is a secretory organ. It is composed of a mass of glia cells and fibers with a very poor blood supply. That the middle lobe pours a secretion into the posterior lobe and through it into the third ventricle has been apparently disproven. The hyalin and colloid masses are merely degenerative products increasing with age. We have therefore no evidence that pituitrin is anything else than a pharmacologically very interesting extract. Oehme and Oehme, who came to the same conclusions, point further that pituitary extract inhibits the action of theocin and the effect of theocin is not increased in diabetes insipidus as it should be if a state of hypopituitarism existed.

We may add to the consideration that the action of pituitary extract is on the kidney, that there is evidence that diabetes insipidus is not due to any defect in the kidney, even functional (thirst may precede the polyuria). Besides, even clinically, pituitrin is not a specific remedy for diabetes insipidus. Cases have been reported in which the injection of pituitrin did not relieve the thirst and in which there was a marked retention of urea. We have recently had opportunity to observe two patients in one of whom pituitrin not only did not relieve the thirst but produced an extreme dilution of the blood (fall of the blood urea nitrogen from 12 to 6 mg. on the day following the injection of 2 c.c. pituitary extract in four doses) and in the other an extreme edema and increase of weight of 5 kg. in twelve hours. The first case was a giant with a metabolism —15 (P.B.B.H., Surg. No. 14,377), the other a boy, aged 17, with polydactylism and other signs of degeneration (P.B.B.H., Surg. No. 14,508).

What, then, is the essence of diabetes insipidus? A prolonged polyuria may theoretically be due to a primary polydipsia, a simultaneous polydipsia and polyuria, or a primary polyuria. The following causes may play a rôle: (a) polydipsia by "unjustified" thirst (psychic), (b) polydipsia by justified thirst as it can be produced experimentally as a consequence of a period of daily exaggerated intake (Veil,[31] Regnier,[32]), (c) simultaneous polydipsia and polyuria as it can be produced by a perturbation of the chemical (diabetes mellitus) or physicochemical regulation of the body fluids, (d) polyuria due to a disturbance of some hormone regulation of the kidney, (e) polyuria due to permanent nervous or vasomotor disturbance of the kidney, (f) functional inability of the kidney to concentrate inducing a compensatory polyuria, (g) polyuria due to anatomic lesion of the kidney. Naturally, such an enumeration is purely artificial. We have no proof that these different conditions may be realized. We may immediately exclude "a" and "g" from our dogs as they are also from the definition of diabetes insipidus. Practically the discussion in later years has been concentrated on two explanations: one which considered the polyuria as a compensatory one due to the inability of the kidney (anatomically normal) to concentrate and the other which considered it an obligatory polyuria due either to a renal or to an extrarenal factor.

The teleological hypothesis of the inability of the kidney to concentrate has been vigorously criticized (Veil[31]). In 1914 Aubertin and Ambard[33] showed that the kidney in diabetes insipidus concentrates. But, nevertheless, recent authors such as Leschke,[2] although recognizing the value of the criticism, point out that it is impossible in diabetes insipidus to make the kidney reach a normal concentraton. The argument often given that in experiments of thirst there may be a concentration of the blood proves simply that the water of the tissues had not the time to replace the water lost. It is the same concentration which may occur in severe diarrhea or sweating with the normal kidney.

We come, then, to a consideration of the possibility of an obligatory polyuria due either to renal or extrarenal factor. We bring evidence that experimental diabetes insipidus is independent of the nervous (if there be such) and vasomotor regulation of the kidneys. It persists after denervation and the denervation produces its usual effects. There is a summation of the two polyurias which shows well their independence. Although the significance of this fact is not yet clear it must be remembered also that it was possible to produce a marked puncture polyuria in a nephritic dog.

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31. Veil: Deutsch. Arch. f. klin. Med. **119**:376, 1916; Biochem. Ztschr. **91**: 1918; Veil and Spiro: München. med. Wchnschr., 1918, p. 1119.
32. Regnier: Ztschr. f. exper. path. u. Therap. **18**:139, 1916.
33. Aubertin and Ambard: Bull. et mém. Soc. méd. d. hôp. de Paris, 1914.

These negative facts lead us to the consideration of an external factor. We bring now the positive fact that the polyuria can be preceded by the thirst. It is not necessarily preceded by it. The polyuria may appear and persist without any intake of water. But at any rate the polydipsia is not consecutive to the polyuria. The only possible way to reconcile these facts is to suppose that the nervous lesion produces at once thirst and polyuria. Such a combination could only arise by a disturbance of the physico-chemical equilibrium of the organism. This hypothesis has already been defended by Veil.

Veil attributes diabetes insipidus to the inability of the tissues to hold water and he tries to give to his hypothesis a chemical basis. But the abnormalities he observed in the chemical constitution of the blood in diabetes insipidus must always be susceptible of a double interpretation: it is very difficult to decide what is cause and what is effect of the excessive loss of water. In recent works, Berglund,[34] and Bauer and Aschner [35] contested the conclusions of Veil and showed that all the differences observed in the blood between normal individuals and cases of diabetes insipidus (e. g., after injection or ingestion of sodium chlorid) could be simply explained by the excessive loss of water in the latter. They found no evidence of a change in the permeability of the vessels for salt. But the failure of the chemical proof of an extrarenal factor is not surprising if we remember that the sensitiveness of the kidney to changes in the blood far surpasses the most accurate biochemical methods (Haldane and Priestly). This is proved by the well known fact that no modification can be found in the blood after intake of water, but there is an immediate diuresis.

It is actually proven that thirst is dependent not on the state of the blood but of the tissues. Cannon [36] has suggested that the dehydration of the tissues causes arrest of the salivary secretion and the dryness of the throat consequently stimulates the nerve endings producing thirst. Therefore, it is interesting but probably unimportant to note also that the center which we traumatize to produce diabetes insipidus in dogs is an important gustatory center (Herrick [15]).

SUMMARY

The intimate mechanism of diabetes insipidus is unknown. It is provoked with certainty by a lesion of the postinfundibular region of the hypothalamus. There is evidence that such a lesion produces both polydipsia and polyuria, and the polydipsia may precede. Experimental diabetes insipidus persists after denervation of the kidney and cannot, therefore, be attributed to a disturbance of its nervous or vasomotor

34. Berglund: Studier över Koksaltomsättningens, Stockholm, 1920.
35. Bauer and Aschner: Wien. Arch. f. inn. Med. **1**: 1920.
36. Cannon, W.: Croonian Lecture, Proc. Roy. Soc. Lond. **90**B:283, 1918.

regulation. We have no evidence of any hormone regulating the kidney, especially a pituitary hormone. The kidney conserves its ability to concentrate. All these facts point to an extrarenal factor as the essence of diabetes insipidus and it is certainly not a coincidence that this condition is accompanied both in clinical and experimental cases by other metabolic disturbances.

PATHOGENY OF ADIPOSOGENITAL DYSTROPHY

We have given proof that it is possible to provoke the cachexia "hypopyseopriva" and the adiposogenital syndrome (together with a permanent diabetes insipidus) by puncture of the postinfundibular region of the hypothalamus without touching the pituitary. The integrity of the gland and of its vascular connections was verified histologically beyond question. The possibility of this has been before asserted (Aschner,[7] Camus and Roussy [17, 18, 20]) with strong arguments in support, but positive proof was never given because of the technic employed. Besides, Aschner who in 1912 claimed that acute genital atrophy without "Fettsucht" was due to extensive lesion of the tuber cinereum seems to have abandoned the idea in 1916 [13] and attributed all the metabolic disturbances to lesion of the anterior lobe of the pituitary. We show that not the extent but the location of the lesion is all important. The lesion can be so small as to be invisible to the naked eye.

The question immediately arises: Cannot these symptoms nevertheless be due to the pituitary by a disturbance of its innervation? The same question was discussed in relation to diabetes insipidus. We believe that it must be answered negatively here also. It must not be forgotten that the only nerve fibers known to go to the pituitary come from the superior cervical ganglia (Dandy,[37] and Berkeley [38]) and removal of these ganglia does not lead to any of these symptoms. Furthermore, pituitary symptomatology has been built up by direct experiments on the gland where minute lesions of the hypothalamus, even contusions which later would not be discoverable with the microscope in hematoxylon and eosin sections were not and could not be taken into account. The situation of these nervous centers immediately adjacent to the pituitary is such that any manipulation of the gland suffices to injure them, as is seen by the occurrence of polyuria (Crowe, Cushing and Homans [21]). Therefore, it is not surprising that even the most careful extirpations of the pituitary (Crowe, Cushing and Homans) produce either quick death or cachexia or adiposity and genital atrophy. It is a strange fact that Aschner, who was the first to recognize the importance of the tuber cinereum, did not try by control experiments to determine with certainty what symptoms following

37. Dandy: Am. J. Anat. **15**:333, 1913.
38. Berkley: Brain **17**:515, 1894.

removal of the pituitary were due to lesion of nervous centers. In his experiments on puppies Aschner obtained in successful cases adiposogenital dwarfism. Of course he gave as arguments against a nervous lesion in these cases the absence of glycosuria and polyuria. But we know that although a hyperglycemia is probably constant, glycosuria is much less frequent after puncture in this region than polyuria. And Camus and Roussy say that polyuria is much more difficult to obtain in young animals.

Besides Aschner does not give any details concerning the immediate symptoms following operation. He had a large immediate mortality from lesion of the tuber cinereum as he himself admits (four out of six animals). In almost every macroscopic verification the infundibulum was adherent to the base of the skull and in the only microscopic verification given of one adiposogenital dwarf there was evident nerve fiber degeneration and round cell infiltration in the tuber. It is surprising that Aschner, attributing the immediate fatal symptoms and acute genital atrophy in adults to lesion of the tuber, should attribute the adipososgenital dwarfism of the few surviving animals to removal of the pituitary.

If we except naturally the arrest of growth the syndrome observed in young animals after extensive lesion of the pituitary is identical with that seen in adults (genital atrophy, adiposity, tolerance for sugar, absence of adrenalin effect). It would be incredible that such identical syndromes should be due in the young to lesion of the pituitary and in adults to a nervous lesion. Experimental lesions in the hypothalamus of puppies are therefore highly desirable.

Quite recently Lereboullet, Mouzon and Cathala [39] have published a case of adiposogenital dwarfism with a suprasellar tumor and integrity of the pituitary, histologically established. The recent experiments of Smith [40] and others who succeeded in causing stunting of growth in young tadpoles by removal of the pars buccalis of the hypophysis seem conclusive until one remembers the resultant maldevelopment of the adjacent nervous tissue. It is apparently not with impunity that the normal biostactic relations of the brain may be disturbed in the developing embryo.

What, then, is the function of the pituitary? It is impossible to admit that an organ with such a highly differentiated glandular structure as the pars buccalis should not have a function at some period of life or at least at some period in the development of the vertebrate phylum. But we must admit that we have little actual knowledge of its functional significance in the adult mammal. The numerous cases published of destruction of the pituitary without symptoms point

39. Lereboullet, Mouzon and Cathala: Rev. neurol. **28**:154, 1921.
40. Smith: Wistar Inst., Pub. No. 11, 1920.

in this direction. The progressive dwindling of the pars infundibularis with cystic degeneration until in man it is hardly discoverable by aid of the microscope points in the same direction.

Have we any evidence of a hyperfunction of the pituitary? The question of acromegaly and giantism is still unresolved. The frequency of hypertrophy or adenoma of the pituitary, as Marie was the first to point out, seems to point to a functional disturbance of the gland. But how many puzzling contradictions exist (acromegaly without any demonstrable pituitary lesion [Yamada [41]] etc.). It should be remembered that feeding experiments have failed to reproduce the syndrome (see however the recent work of Uhlenhuth [42] in salamanders). These feeding experiments may have great interest for the physiology of nutrition but it is dangerous to draw from them conclusions concerning the function of endocrine organs. Besides, tissue hypertrophies may be produced by a purely nervous lesion (cheiromegaly in syringomyelia). Therefore, it is not impossible that the acromegalic syndrome may be due to an effect of the pituitary growth on the hypothalamic centers. It is very suggestive in this regard that tumors of the pineal region produce metabolic and sexual disturbances of a hypertrophic nature. The fact that these troubles must be due to pressure on neighborhood centers is well shown by the constant occurrence in the syndrome of symptoms due to various lesions of the brain and cranial nerves and in some cases by the development of the peculiar symptoms such as genital hyperplasia and adiposity in the final stages of the disease (Marburg).

As to the function of the posterior lobe the experimental evidence is unequivocal. Its removal causes no symptoms. Moreover, its structure is nonglandular. Camus and Roussy are quite justified in speaking of it as an atrophied nervous lobe. But we must reckon with the fact that from it may be extracted a very active substance, pituitrin (the origin of pituitrin in the posterior lobe and not in the pars infundibularis we accept as an established fact). It is difficult to conceive that such a substance, which is found in the pars nervosa of all vertebrates, should be without significance. Since the pars nervosa is composed almost wholly of glia, it is quite possible that this material may be extracted from the glia anywhere.

We have, on the other hand, a body of facts which show that in the hypothalamus are important nervous centers controlling manifold visceral regulations. Their anatomic connections are very imperfectly known. They are intimately connected with the olfactory and gustatory (Herrick [15]) systems, specialized parts of the visceral nervous system. There is some anatomic evidence also that these centers have important connections with the general visceral system, for retrograde

41. Yamada: Mitt. a. d. Med. Fakult. d. K. Univ. zu Tokyo **18**:411, 1917.
42. Uhlenhuth: J. Gen. Physiol. **3**:347, 1921.

changes occur in their nuclei after section of the sympathetic trunk in the neck (Huet [36]) and after destruction of the sympathetic nucleus of the vagus (Brugsch, Dresch and Lewy [16]).

The physiology of the hypothalamus is also beginning to be known although the experiments have usually been acute. After lesions experimentally produced have been noted disturbance of heat regulation, dilatation of the pupil, change in the pulse and respiratory rate, glycosuria, transitory polyuria, polypnoea, etc. We believe that we bring proof also that trauma of this region may cause in addition, depending on the site and size of the lesion, permanent polyuria, adiposogenital dystrophy, cachexia and even rapid death.

The mechanism of production of the adiposity and genital regression is completely obscure. The two symptoms are in some form constantly associated, which justifies the term adiposogenital dystrophy. The fact that the adiposity is out of proportion to the adiposity of the castrate excludes the possibility of considering it as a simple consequence of the genital atrophy. Besides, the adiposity, as is well known, is only one element of a far-reaching metabolic disorder (apathy, low basal metabolism, high tolerance for sugar and epinephrin, arrest of growth in the young, etc.). Furthermore, we have seen that diabetes insipidus is probably also a metabolic disturbance.

Through what intermediary, nervous or endocrine, does the lesion of the hypothalamus produce such disorders? It is at present impossible to answer the question. It must be simply pointed out that (except naturally for the genitals) it is difficult to advocate a disturbance of any particular endocrine organ, including the hypophysis, these organs being histologically normal. The difficulty of explanation is especially acute for the genital atrophy. We have seen that the degeneration of the germinal cells may appear extremely early (Dog 3). Later (Dog 10) there is also a definite sclerosis of the interstitial gland which may account for the late regression of the secondary sex characters and the loss of libido.

Camus and Roussy, assuming that the hypothalamus controls the kidney by a nervous mechanism and pointing to the common embryologic origin of the kidney and sex glands, make the same supposition of a nervous control for the latter. But we came to the conclusion that the diabetes insipidus is not dependent on the nevous control of the kidney.

If such a nervous regulation of the sex glands exist, the nerve fibers on which it depends must leave the central nervous system very high because, so far as we know, in no case of complete transection of the spinal cord, either in man or animals, has an atrophy of the genitalia been observed. The recent work of Kuntz [43] may

43. Kuntz: Anat. Rec. **17**:203, 221, 1919.

point to a nervous trophic regulation of the testes. The author showed that the removal of the inferior mesenteric ganglion in dogs produces a rapid degeneration of the germinal cells of the testes with an hypertrophy of the interstitial cells. The few animals operated on were killed after about three weeks and no details are given concerning their sexual capacity. The author himself attributes the degeneration observed to vasomtor disturbance. Further research along these lines is evidently desirable.

Provisionally we are more inclined to consider the genital atrophy in connection with the invariably accompanying metabolic disorders. The extreme sensitiveness of the germinative cells to toxic influences and to deficient diet (e. g. in vitamins, Allen [44]) is a well known fact, and may perhaps explain the regression of the gonads in the metabolic disorders under discussion. But we realize that such words as "metabolic" merely cover our ignorance and throw little light on the subject.

The establishing of these ideas would do much to clear away the many puzzling contradictions which continue to worry the clinicians; pituitary destruction without pituitary symptoms, pituitary symptoms with integrity of the pituitary, occurrence of diabetes insipidus and adiposogenital dystrophy in encephalitis lethargica whose nuclear election is well known, frequency of occurrence of polyglandular syndromes by lesion of the pituitary region, the paradox of regression of pituitary symptoms by roentgen-ray treatment of pituitary adenomas, treatment which must destroy what little is left of the glandular cells (Béclère [45]).

All these contradictions and many others may be explained by the presence in the brain stem just above the pituitary of an important head ganglion of the visceral nervous system. We believe that the time is not far distant when the neuropathologist will no more think of omitting to examine the hypothalamus than he would the motor cortex.

CONCLUSIONS

In order to distinguish among the symptoms which are commonly ascribed both in clinical cases and in experiments on animals to the lesion or removal of the hypophysis, those which may be due to lesion of the adjacent nervous centers, systematic punctures of the hypothalamus have been made in adult dogs. The lateral route of Paulesco and Cushing has been employed, which gives a perfect exposure of the region and permits avoidance of the hypophysis with practical certainty, contrary to the transsphenoidal procedure hitherto employed for the purpose. The results of the experiments may be summarized as follows:

1. The consequences of the puncture depend strictly on the localization of the lesion and, when the localization is correct, on the extent.

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44. Allen: Anat. Rec. **16**:93, 1918.
45. Béclère: Paris méd. **11**:97, 1921.

2. A lesion, even extremely minute, of the para-infundibular region of the hypothalamus provokes with certitude (in thirteen of thirteen dogs) a polyuria which appears in the first two days. According to the extent of the lesion it varies from a transient one lasting from six to eight days to an apparently permanent polyuria.

3. In the latter case other important symptoms were present, e. g., cachexia "hypophyseopriva," genital atrophy and adiposity.

4. The permanent polyuria has all the characteristics of diabetes insipidus in man, e. g., possibility of concentration when intake of fluids is restricted, when pituitary extract is injected subcutaneously or in the presence of fever, excessive polyuric action to the administration of chlorids, absence of theobromine effect.

5. The thirst may precede the polyuria. In five cases the increase in intake preceded the output by one day, and during several subsequent days there was a marked discrepancy between the intake and output. On the other hand, the polyuria may appear and persist without intake of water, e. g., in comatose animals.

6. The experimental diabetes insipidus does not depend on a disturbance of a supposed nervous or vascular regulation of the kidney. It may be induced in animals whose kidneys have previously been denervated and when present persists after denervation of the kidneys with the same characteristics.

7. Lesion of the tuber cinereum has produced in two dogs a cachexia "hypophyseopriva" with acute genital atrophy and in two other dogs an insidiously developing adiposogenital dystrophy. The integrity of the pituitary was in each case verified histologically. The same dogs had persistent polyuria.

8. An extensive lesion of the tuber cinereum is incompatible with life. The animals either die quickly or after a period of apathy in coma and convulsions.

9. Glycosuria was an inconstant result of the lesion and seemed to depend probably on the state of nutrition of the animal.

10. Lesion, even deep, of the base of the brain outside of the para-infundibular region may produce a glycosuria but never a polyuria, the operative trauma being the same as in the previously mentioned polyuric animals. The relationship of the mamillary bodies to the polyuria is undetermined. Involved in a few cases, they were uninjured in other animals which had nevertheless polyuria and other symptoms.

11. The situation of this important nervous center and the minuteness of the lesion necessary to provoke characteristic symptoms probably explains the results of operations on the hypophysis in both young and adult animals. There is no evidence at present that the lesion acts by the intermediation of the pituitary.

OBSERVATIONS ON GLYCEMIA, GLYCURESIS, AND WATER EXCRETION IN OBESITY *

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Joslin [1] recently emphasized the fact that many diabetics are overweight for their age, sex and height when the diagnosis of diabetes is first made, or have a history of obesity before they develop diabetic symptoms. It has seemed of interest, on this account, to observe the results of an alimentary glucose tolerance test in a series of nondiabetic obese patients in an attempt to determine how many had an abnormally low tolerance, and could, therefore, be classified on laboratory, as well as clinical evidence, as being prediabetic.

For this purpose a group of thirty-two stout persons was studied, consisting of eight men and twenty-four women who came to the Mayo clinic for obesity or for obesity and some secondary ailment which could not definitely be related to diabetes. The urine of each patient was sugar-free on routine examination.

One of the men weighed 370 pounds, one weighed 285 pounds, one 253 pounds, and the others were at least 10 per cent. overweight for their age according to the Medico-Actuarial statistics.[2] The heaviest woman weighed 291 pounds and several others weighed more than 225 pounds. The women, as well as the men, all weighed at least 10 per cent. more than the normal for their respective ages.

The glucose tolerance test was conducted according to the plan of Hamman and Hirschman.[3]

On the day of the test the patient ate no breakfast. A sample of blood and urine was obtained. The patient was given 100 gm. glucose in 500 c.c. lemonade. Samples of blood and urine were obtained thirty minutes later and one hour later. The patient was given 150 c.c. water. Two hours later samples of blood and urine were obtained and the patient was given 150 c.c. of water. Three hours later final samples of blood and urine were obtained. Thus each patient drank 800 c.c. of fluid during the period of study and samples of blood were taken five times.

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1. Joslin, E. P.: The Prevention of Diabetes Mellitus, J. A. M. A. **76**:79 (Jan. 8) 1921.

2. Medico-Actuarial Mortality Investigation. The Association of Life Insurance Medical Directors and the Actuarial Society of America, New York, 1912.

3. Hamman, L., and Hirschman, F. I.: Alimentary Hyperglycemia and Glycosuria as a Test for Sugar Tolerance, Arch. Int. Med. **20**:761 (Nov.) 1917.

The volume of each urine specimen was recorded and each was tested for sugar by Benedict's qualitative method. The blood sugar concentration was estimated by the method of Folin and Wu.[4]

The observations on obese persons were controlled by similar tests made on ten nondiabetic patients of normal weight and on eleven mild diabetic patients. To the nondiabetic patients, however, 0.66 gm. glucose for each pound of body weight was given, and to the diabetic patients a routine dose of 50 gm. glucose was given instead of 100 gm. We were unable to graduate the dosage of glucose on the basis of body weight in the obese, as in the few cases tried such large doses as were necessary caused prompt nausea and vomiting. We did not feel justified in giving more than 50 gm. glucose to our diabetic patients as their urines had all been made sugar-free before their sugar tolerance was tested in this fashion, and we were afraid that larger doses might be harmful.

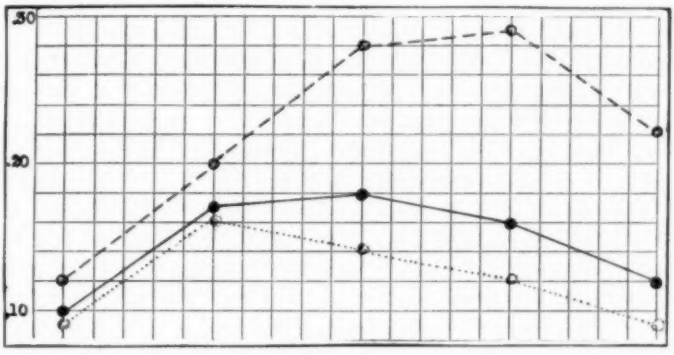

Fig. 1.—Blood sugar curve following the ingestion of glucose in nondiabetic patients, obese patients, and diabetic patients: dotted line, nondiabetic patients; broken line, obese patients; solid line, diabetic patients.

Figure 1 shows composite curves of the blood sugar determinations in each of the three types of cases plotted by averaging all the results.

The average curve in the nondiabetic controls was not remarkable. The highest point in glycemia was reached shortly after the glucose was ingested and such hyperglycemia as occurred disappeared so promptly that the last blood sugar reading was no higher than the first.

The average curve in the diabetic patients was also typical. The blood sugar reading did not reach its maximum and did not return to its original base line as rapidly as in normal patients, and its highest point was much higher than in the control curve.

4. Folin, O., and Wu, H.: System of Blood Analysis; a Simplified and Improved Method for Determination of Sugar, J. Biol. Chem. **41**:367, 1920.

The curve of the patients with obesity is more interesting. It appears to be midway between the normal and diabetic curves, although it approaches the normal shape more closely than the diabetic. It does not suggest that most of the persons in the series according to this test were prediabetic.

When the patients are considered separately, however, certain features are noteworthy. Four patients had a fasting blood sugar above 0.15 per cent. Two of these had a normal type of sugar curve in other respects. The other two gave a reaction to glucose so typical of diabetes as more positively to suggest that they represented an early stage of the disease. The data from these two cases is shown graphically in Figure 2.

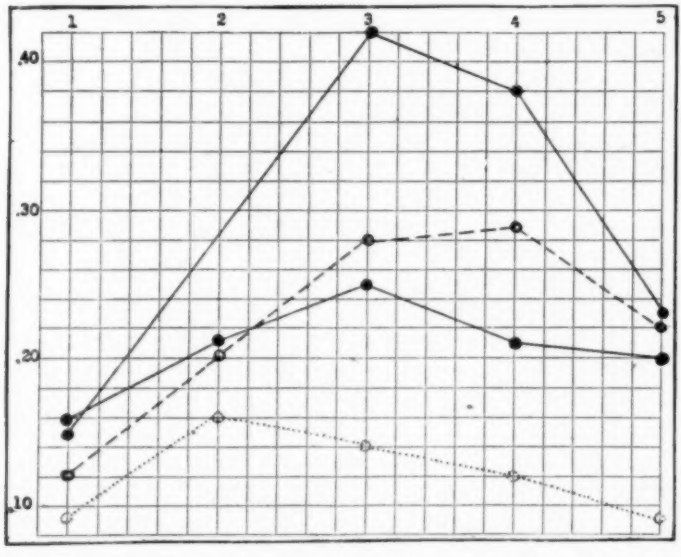

Fig. 2.—Blood sugar curve in two obese patients, suggesting early diabetes.

SYNOPSIS OF CASES

Case 1.—A woman, aged 32, 5 feet tall, had gradually gained from her normal weight of 120 pounds to her present weight of 164. She had no family history of diabetes or obesity. She came to the Clinic for the purpose of losing weight, and had no diabetic symptoms.

Case 2.—A man, aged 49, came to the Clinic because of palsy of cerebral origin; he had no diabetic symptoms except that he had lost 70 pounds in weight during the last fifteen months. His present weight was 196 pounds.

Six patients, while having a fasting blood sugar concentration of 0.12 per cent. or less, had a persistent hyperglycemia following the ingestion of glucose and thus resembled mild diabetes in their type of

reaction. The data from a marked example of this description are shown graphically in Figure 3.

CASE 3.—This patient was a short woman, aged 41, with incontinence due to a urethral stricture. She had gained 29 pounds in the last six months owing to physical inertia and excessive eating. She weighed 204 pounds.

On the whole our results from blood sugar studies on obese patients with reference to the early diagnosis of diabetes mellitus were disappointing. The majority of the thirty-four patients observed had no fasting hyperglycemia and had a nearly normal blood sugar curve following the ingestion of 100 gm. glucose. Marked deviations from normal, suggestive of diabetes, occurred in but few cases. There seemed little evidence for the belief that this test as performed was of marked clinical value, except in rare instances. It is probable, however, that more striking results would be obtainable if the dosage of

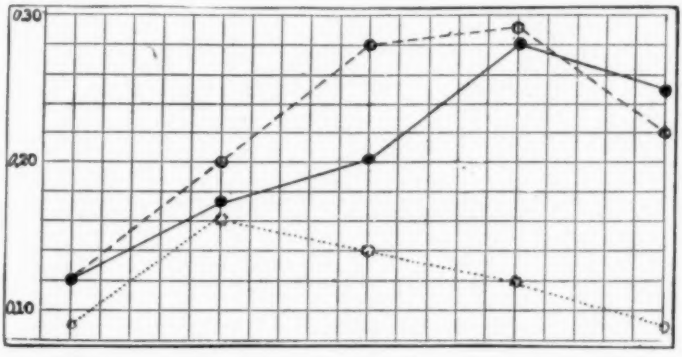

Fig. 3.—Blood sugar curve in one obese patient, suggesting early diabetes.

glucose were made on the basis of body weight and if the sugar solution were administered intravenously according to the method of Woodyatt, Sansum and Wilder.[5]

Sugar excretion was estimated quantitatively in seventeen obese, four nondiabetic, and five diabetic patients. The total sugar eliminated after the sugar was ingested was determined by the method of Benedict,[6] or of Benedict and Osterberg [7] on the urine excreted during the period of observation.

5. Woodyatt, R. T.; Sansum, W. D., and Wilder, R. M.: Prolonged and Accurately Timed Intravenous Injections of Sugar, J. A. M. A. **65**:2067 (Dec. 11) 1915.

6. Benedict, S. P.: The Detection and Estimation of Glucose in Urine, J. A. M. A. **67**:1193 (Oct. 7) 1911.

7. Benedict, S. P., and Osterberg, E.: A Method for the Determination of Sugar in Normal Urine, J. Biol. Chem. **34**:195, 1918.

The amount of sugar excreted by the four nondiabetic patients varied between 64 and 467 mg. with an average of 233 mg. This, however, was in sharp contrast to the sugar excretion of the five diabetic patients who all excreted much larger amounts.

The excretion of sugar by the obese patients was of two distinct types. Eleven patients excreted a normal or less than the average normal amount of sugar following the ingestion of 100 gm. glucose, and six patients excreted an abnormally large amount. The essential features of these observations are recorded in Table 3.

With two exceptions, all of the patients who excreted small amounts of sugar in the urine had a normal glycemia curve. The two remaining patients both had a diabetic type of glycemia so that in one the last

TABLE 1.—EXCRETION OF SUGAR IN NONDIABETIC PATIENTS

Case	Sex	Age	Weight, Kg.	Total Sugar Excretion, Mg.	Sugar, Mg. for Each Kg.
1	F	35	52.2	64	1.2
2	M	42	69.5	154	1.0
3	M	56	71.7	246	3.4
4	F	18	54.5	467	8.6
Average		38	62.0	233	3.8

TABLE 2.—EXCRETION OF SUGAR IN DIABETIC PATIENTS

Case	Sex	Age	Weight, Kg.	Total Sugar Excretion, Mg.	Sugar, Mg. for Each Kg.
1	M	48	76.8	2,165	28.1
2	M	40	77.2	3,920	50.7
3	M	55	91.0	5,500	60.5
4	M	47	59.1	10,300	175.0
5	F	20	43.6	12,092	275.0
Average		40	69.5	6 795	97.8

sugar reading was 0.25 per cent. and in the other the first and fifth samples were within normal limits, but the three middle specimens gave readings of 0.18, 0.23 and 0.22 per cent, respectively. There was no evidence of any renal impermeability in these cases, though certain ones had symptomatic evidence of polyglandular insufficiency. These data are recorded in Part I of Table 3.

The fact that so many patients of this group excrete less than the average normal amounts of glucose after taking 100 gm. pure sugar is noteworthy. It could be explained on the ground that the dose of sugar used per unit of body weight was small and that, therefore, the excretion of sugar was correspondingly small. On the other hand, the metabolism of obesity has received considerable investigation. Most authors follow von Noorden's classification of the two types of

obesity.[8] The first depends on a normal metabolism with adiposity developing through an increased food intake and a diminished energy expenditure. The second depends on a true slowing of metabolism. There is abundant evidence to explain the cause of the first type of case. There is less evidence in favor of the second. However, certain fat persons undoubtedly show a tendency to gain weight despite an intelligent regulation of diet and exercise, and others fail to lose weight when taking a low calory diet over a long period of time. These facts suggest an abnormal metabolism as the true cause of the condition.

TABLE 3.—Excretion of Sugar in Obese Patients

Case	Sex	Age	Weight, Kg.	Onset of Obesity	Total Sugar Excretion, Mg.	Sugar, Mg. for Each Kg.
				PART I		
1	F	55	110.0	Gradual	44	0.4
2	F	39	87.4	.....	106	1.2
3	F	32	132.1	.....	107	0.8
4	F	21	109.0	34 kg. gain in one year	138	1.3
5	F	30	89.0	15 kg. gain in six months	142	1.6
6	F	54	79.5	.....	146	1.8
7	M	45	86.4	.....	163	1.9
8	F	62	91.0	Gradual	211	2.3
9	F	41	92.8	15 kg. gain in eight months	314	3.4
10	F	59	102.0	Gradual	376	3.7
11	M	52	168.0	Gradual	428	2.6
Average	.....	44	104.0	.....	198	1.9
				PART II		
1	F	43	91.0	15 kg. gain in six months	1,019	11.2
2	M	42	91.0	Gradual	1,208	13.3
3	F	47	72.6	Gradual	2,794	38.4
4	F	26	88.5	Gradual	3,737	42.2
5	M	56	99.5	Gradual	4,950	49.5
6	F	32	74.5	Gradual	7,850	105.3
Average	.....	40	86.0	.....	3,593	41.7

Means [9] recently investigated the basal metabolism in obesity, using the Benedict apparatus and analyzing his data on the basis of the DuBois formula. He found no characteristic change in basal metabolism in the twelve cases which he studied, and he found that the specific dynamic action of protein was normal.

Waldvogel [10] attempted to study one phase of fat metabolism in obesity by injecting beta-oxybutyric acid subcutaneously and following

8. Von Noorden, C.: Zur Frühdiagnose des Diabetes mellitus, Verhandl. d. Congr. f. inn. Med. **13**:481, 1895.

9. Means, J. H.: Studies of Basal Metabolism in Obesity and Pituitary Disease, J. M. Research **32**:121, 1915.

10. Waldvogel: Zur Pathogenese der Fettsucht, Deutsch. Arch. f. klin. Med. **89**:342, 1907.

its excretion in the urine and expired air. His evidence is not convincing, although his conclusions are interesting. He found a larger excretion of acetone in the expired air and urine of his obese patients than in control patients who had received the same dosage of acid, and, therefore, believed that in adiposity there was some disturbance in intermediary fat metabolism by which beta-oxybuturic acid was not burned to its usual completion.

Wilder and Sansum [11] reported on the sugar tolerance of a case of myxedema and five cases of hypophyseal disease which were studied by continuous intravenous injection. They found no increased tolerance in these cases by this method and concluded that the increased tolerance of such patients for sugar given by mouth is due to a retarded absorption from the bowel rather than to any anomaly of intermediate metabolism. These authors obtained the same results in a few cases of obesity studied at that time.

Some of our observations suggest, in spite of this evidence to the contrary, that certain obese patients may store sugar with abnormal ease or else burn it with unusual thoroughness. At least this explanation would account for our findings in those patients without evidence of renal impermeability, who excreted an abnormally small amount of sugar in the urine following the ingestion of glucose, and which must have absorbed the sugar from the stomach as was shown by the temporary rise in the concentration of circulating sugar. A reaction of this sort by sparing protein or fat metabolism might readily be a factor in the development of "endogenous" obesity. It requires more thorough investigation.

The observations on the patients who excreted abnormally large amounts of sugar following the ingestion of glucose are summarized in Part II of Table 3. All had a glycemia curve suggestive of mild diabetes. It would seem justifiable to believe that obese patients who respond to a standard dose of glucose by a curve of glycemia suggestive of diabetes, and by an increased total excretion of urinary sugar, should be treated at the outset for diabetes as von Noorden [12] found that of fifteen such patients whose course he followed for a long time, five were known to develop genuine diabetes later.

Several of our patients exhibited an interesting peculiarity in relation to the excretion of urine following the rapid intake of 800 c.c. fluid. The nondiabetic controls excreted between 100 c.c. and 800 c.c. of urine under these conditions with an average excretion of 418 c.c. Of thirty obese patients, three excreted less than 100 c.c. urine in the

11. Wilder, R. M., and Sansum, W. D.: *d*-Glucose Tolerance in Health and Disease, Arch. Int. Med. **19**:311 (March) 1917.

12. Von Noorden, K. H.: Metabolism and Practical Medicine, Chicago, W. T. Keener Company, 1907.

two hours' observation time, and only four excreted more than the average normal of 418 c.c. Of the seven diabetic patients, on the other hand, only two excreted less than 300 c.c. urine in two hours, and the others excreted more than 500 c.c., so that the average of the group was 501 c.c. As a general rule, obese patients with normal blood sugar curves and without an exaggerated glycuresis excreted small volumes of urine, while those with a diabetic curve of glycemia and with an increased excretion of sugar had a relatively large volume of urine. Such oliguria in obesity has been explained by Labbé and Furet [13] on the basis of chlorid retention and by Grafe,[14] who found that interference with the water balance is not uncommon and is often dependent on interference with the thyroid mechanism for regulating intracellular water metabolism. The recent work of Larson, Weir and Rowntree [15] suggests that the pituitary gland, as well, may play a part in this mechanism.

CONCLUSIONS

Obese patients show characteristic changes in sugar and water metabolism which may be of importance in subsequent treatment. Certain patients show a relatively normal curve of glycemia following the ingestion of 100 gm. glucose. These patients tend to excrete small volumes of urine and small quantities of sugar. They do not appear to retain sugar because of an impermeable kidney but rather to have some disturbance in sugar and water metabolism which may be related to an endocrinopathy. It seems possible that these patients burn or store sugar with unusual rapidity, a reaction which may have a sparing influence on fat and protein metabolism and may be a factor in the development of adiposity. The effect of water retention in these patients is not known. They are probably not likely to develop subsequent diabetes, and should be treated for obesity and endocrine disease, if the existence is demonstrable.

On the other hand, another group of obese patients has a curve of glycemia following the ingestion of 100 gm. glucose which resembles that of mild diabetes. These patients excrete abnormally large amounts of glucose in their urine over a measured interval of time and excrete normal amounts of urine or may even have a slight diuresis. This type of case probably represents early diabetes and should be treated accordingly.

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13. Labbé, H., and Furet, L.: Les troubles de l'élimination chlorurée urinaire; facteurs d'obésité, Presse méd. **13**:809, 1905.

14. Grafe, E.: Zur Pathologie und Therapie der sogenannten "konstitutionellen" Fettsucht, Deutsch. Arch. f. klin. Med. **133**:41, 1920.

15. Larson, E. E.; Wier, J. F., and Rowntree, L. G.: Studies in Diabetes Insipidus, Water Balance and Water Intoxication, Tr. Assn. Am. Phys., 1921.

The fasting blood sugar estimation or the glycemia curve, alone, is of little significance and is probably of less importance than the determination of glycuresis.

A sugar tolerance test in obese patients which includes a blood sugar curve and quantitative measurement of sugar and fluid output affords valuable diagnostic and therapeutic information.

A STUDY OF SIGNIFICANT CHEMICAL CHANGES IN THE BLOOD COINCIDENT WITH MALIGNANT TUMORS *

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In 1897 Schopp and Moraczewski [1] concluded from their studies on urine that the development of carcinomatous growths in the human organism was characterized by a retention of nitrogen. This minus balance was attributed to an increased demand for nitrogen by the malignant tumor. More recent chemical studies on the blood in malignancy, while confirming this observation, have at the same time proffered a different interpretation of the nitrogen retention. The most comprehensive analyses of the blood in malignancy have been placed on record within the last year by Theis and Stone.[2] Their studies included observations on the nonprotein, urea and amino-acid nitrogen, and the uric acid and sugar in a series of 189 cases, representing a wide range of type and location of malignant neoplasms. They have reported subnormal values for nonprotein and urea nitrogen, particularly in the rapidly growing tumors of the breast and uterus, and an amino-acid nitrogen slightly above normal. The uric acid was found to be normal or subnormal in all instances except two cases of melanoma. In the selection of their cases these authors state that care was taken to exclude all patients with involvement of renal function, but it is not clear on what evidence the diagnosis of renal involvement was made. On the basis of similar values for these components of the blood in pregnancy reported by other observers, an interesting analogy has been suggested by Theis and Stone between the influence of development of malignant tumors and of the embyro on the concentration of the nonprotein nitrogenous constituents of the blood of the host. The comparative decrease in the amounts of these compounds in the circulating blood has been ascribed to an increased need for nitrogen for the new growth, whether it be malignant tumor or embryo.

A number of contradictory observations have been recorded on the acid-base equilibrium of the blood in malignancy. Moore and Wilson [3]

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* Read in part before the American Gastro-enterological Society, Boston, June 7, 1921.

1. Schopp and Moraczewski: Ztschr. f. klin. Med. **33**:385, 1897.
2. Theis and Stone: J. Cancer Research, **4**:349, 1919.
3. Moore and Wilson: Bio-Chem. J. **1**:297, 1906.

report in the blood serum in malignancy an increase in basicity, which was found present in early cases and was not affected by the removal of the growth. This alleged increased basicity the authors state is not due to the disease, but rather to the advanced age of their patients. More recently, Menten,[4] using the Michaelis method, found a normal or decreased alkalinity in only three or four out of a series of seventy patients with malignant disease, the remaining cases showing an increased alkalinity. The increased alkalinity was particularly manifest in carcinomas of the viscera but less marked in external tumors. The administration of sodium bicarbonate provoked a more rapid growth of the malignancy. Peiper,[5] on the contrary, has observed a decrease in the alkalinity of the blood in cases of carcinoma, particularly where there is evidence of cachexia.

The concentration of sugar in the blood in malignancy probably has received more attention than any other component. Trinkler [6] has found in all cancerous patients examined, a hyperglycemia which was more manifest in carcinomas of the internal organs than in carcinomas of the skin or mucous membranes. This increase in blood sugar, however, bears no relation to the development of cachexia. Cammidge [7] attributes the hyperglycemia associated with carcinomas to a disturbance of the endocrine function. Of the fifty-three patients with malignant tumors examined by Benedict and Lewis,[8] 36 per cent. revealed a marked increase in blood sugar, from 0.12 to 0.16 per cent., and forty-nine per cent. showed a tendency to a hyperglycemia. The blood was drawn in these cases three hours after the taking of food. The hyperglycemia was attributed by these authors to a constant demand of the growing tumor for carbohydrate. Rohdenburg, Bernhard and Krehbiel [9] found in miscellaneous cases of malignant tumors normal blood sugar values, but after the ingestion of 100 gm. glucose they obtained hyperglycemias persisting for from three to four hours. The blood sugar curves obtained bore no relation to the location of the tumor, or its nature (carcinoma or sarcoma) but closely simulated curves obtained after epinephrin injections, or in cases of hyperthyroidism. The suggestion is made by them that a probable explanation of the development of malignant neoplasms may be found in a disturbance of endocrine function. It is worthy of note, however, that glycosuria was not present in any case. A large number of the patients examined had tumors of the gastro-intestinal tract. No allowance was made by

4. Menten: J. Cancer Research **2**:179, 1917.
5. Peiper: Virchow's Arch. f. path. Anat. **116**:337, 1888.
6. Trinkler: Centralbl. f. d. med. Wissensch. **28**:498, 1890.
7. Cammidge: Practitioner **104**:131, 1920.
8. Benedict and Lewis: Med. Rec. **86**:650, 1914.
9. Rohdenburg, Bernhard and Krehbiel: J. A. M. A. **72**:1528 (May 24) 1919.

these authors for the rate of absorption of the glucose, or for a possible renal involvement. Friedenwald and Grove [10] in like manner obtained characteristic blood sugar curves in carcinomatous patients after taking 100 gm. glucose. The control specimens show a mild hyperglycemia, which after the ingestion of the glucose rose to 0.24 per cent. in forty-five minutes and during a period of two hours did not drop below 0.20 per cent. The curve obtained in malignancies of the gastro-intestinal tract differs from those observed in carcinomas of other regions, and therefore, may be used as an aid in differential diagnosis. A hyperglycemia associated with an increased diastatic activity of the blood was frequently found by De Niord and Schreiner [11] in a large series of cancerous patients.

In order to determine the systemic effects of malignant neoplasms on the human organism, we began about two years ago a study of the chemical changes in the blood of cancerous patients, and this study has been pursued continuously since that time. Although no specific change in the chemical composition of the blood due to the malignancy has been observed, nevertheless, we believe the results obtained warrant the deduction of definite conclusions of practical value. Our studies comprise analyses of the blood for urea nitrogen, and in some instances for nonprotein nitrogen, uric acid, creatinin, sugar and carbon dioxid combining power. The diastatic activity of the blood has also been determined in special cases. In all of these analyses the methods recently described by Myers [12] have been followed. The specimens of blood were obtained in the morning before breakfast. The data also include the phenolsulphonephthalein excretion, the occurrence of protein and casts in the urine, and the blood pressure. The principal clinical manifestations of the cases, having a possible bearing on the chemical blood findings have been noted under remarks. We have included in this series those cases in which the diagnosis of malignancy has been confirmed by operation, or by necropsy with subsequent histologic examination of the tissue. However, a few cases of carcinoma of the stomach came neither to operation nor necropsy, but in these instances there can be no question of the correctness of the diagnosis established by clinical findings, roentgenologic examination and chemical analysis of the gastric contents. Finally, we wish to emphasize the fact that the patients studied by us were not in a moribund state. On the contrary, they were patients who had presented themselves, many for the first time, at a general hospital principally for diagnosis.

10. Friedenwald and Grove: Am. J. M. Sc. **160**:313, 1920.
11. De Niord and Schreiner: Arch. Int. Med. **23**:484 (April) 1919.
12. Myers: Practical Chemical Analysis of Blood, St. Louis, 1921.

CHEMICAL CHANGES IN THE BLOOD COINCIDENT WITH MALIGNANT NEOPLASMS

No	Case	Age	Blood Analyses						Phenolsulphonephthalein per Cent. in 2 Hrs.	Urine		Blood Pressure		Days Under Observation	Remarks
			Uric Acid	Urea N	Creatinin	Diastatic Activity	Sugar	CO_2 Combining Power		Protein	Casts	Systolic	Diastolic		
1	H. T.	50	4.6	15	1.9	..	0.12	..	..	—	—	....	..	14	Carcinoma of breast
2	J. D.	39	....	15	2.2	..	....		..	—	—	....	..	14	Carcinoma of breast
3	M. D.	38	2.8	15	2.1	..	0.12	..	..	—	—	....	..	16	Carcinoma of breast
4	M. B.	36	4.2	17	....	..	0.13	..	..	—	—	....	..	14	Carcinoma of breast
5	M M.	62	....	46	5.4	..	0.14	25	..	—	—	....	..	2	Carcinoma of breast; died from postoperative acidosis
6	C. S.	48	3.2	12	1.6	..	0.13	..	..	—	—	130	48	4	Multiple sarcoma
7	S. B.	45	4.2	13	1.9	..	0.12	..	..	—	—	130	68	67	Multiple sarcoma; moderate anemia
8	A. M.	45	....	29	1.7	..	0.12	..	..	—	—	....	..	21	Lymphosarcoma of right groin
9	E. H.	75	....	13	1.5	..	0.11	..	..	—	—	....	..	20	Carcinoma of tongue
10	W. L.	57	....	41	2.7	..	0.10	..	..	+	—	....	..	56	Carcinoma of larynx
11	J. F.	44	5.1	16	1.7	..	0.18	..	40	+	—	140	80	37	Carcinoma of lungs; necropsied
12	J. P.	40	4.5	29	3.0	..	0.13	..	..	—	—	140	90	..	Carcinoma of lungs; necropsied
13	J. V.	67	....	21	3.0	..	0.11	..	56	+	+	100	60	..	Carcinoma of esophagus; postoperative uremic death
14	W. W.	63	10.1 8.0	114 27	6.0 3.5	.	0.26	52	..	—	—	....	..	3	Carcinoma of esophagus and cardia. Died following operation
15	S. C.	50	6.8	36	2.4	..	0.18	52	40	+	—	100	70	10	Carcinoma of esophagus; uremic death after gastrostomy
16	M. K.	45	....	11	2.1	..	0.16	..	60	—	—	150	80	22	Inoperable carcinoma of stomach; laparotomy
17	L. B.	51	....	12	2.0	..	0.11	..	55	—	—	....	..	21	Inoperable carcinoma of stomach; laparotomy
18	F. T.	60	....	13	1.8	..	0.12	..	52	—	—	120	70	10	Carcinoma of stomach; treatment medical
19	M. C.	64	3.6	14	2.0	..	0.12	..	..	+	+	120	90	10	Carcinoma of stomach; treatment medical
20	L. T.	42	....	14	2.1	..	0.11	..	..	—	—	....	..	34	Carcinoma of stomach; pylorectomy; improved
21	T. E.	43	....	14	1.9	..	0.12	..	..	—	—	....	..	20	Carcinoma of greater curvature and omentum; laparotomy
22	A. Y.	57	....	15	2.0	..	0.11	..	..	+	—	....	..	29	Carcinoma of pylorus; improved after gastro-enterostomy
23	J. M.	57	4.0	15	1.8	..	0.12	..	..	—	—	....	..	14	Carcinoma of stomach; treatment medical
24	V. C.	50	....	15	2.2	..	....	..	..	—	—	....	..	..	Carcinoma of stomach; improved after gastro-enterostomy
25	A. V.	67	....	16	2.5	..	0.12	..	45	—	—	....	..	26	Carcinoma of stomach; treatment medical
26	A. M.	43	....	17	1.4	..	0.11	..	56	—	—	....	..	14	Carcinoma of stomach; laparotomy
27	M. Z.	68	5.4	17	2.0	..	0.12	..	..	—	—	118	75	13	Carcinoma of stomach; improved after gastro-enterostomy
28	F. H.	66	4.1	17	2.1	..	0.10	..	..	+	—	....	..	18	Carcinoma of stomach with metastases to liver; laparotomy
29	A. D.	63	....	17	1.9	..	0.09	..	..	+	+	120	70	16	Inoperable carcinoma of stomach; laparotomy
30	I. K.	58	....	11	1.8	..	0.11	..	85	+	+	....	..	25	Carcinoma of stomach; treatment medical
31	I. S.	56	4.7	19	2.6	..	0.09	..	..	—	—	....	..	27	Inoperable carcinoma of stomach; laparotomy
32	H. M.	49	....	19	2.5	..	0.16	..	..	+	—	....	..	24	Carcinoma of pylorus; improved after gastro-enterostomy
33	S. M.	55	....	22	2.3	..	0.11	..	56	—	—	100	60	30	Carcinoma of stomach; died following operation
34	M. P.	58	4.0	22	3.0	..	0.12	..	..	—	—	130	98	27	Inoperable carcinoma of stomach; laparotomy

35	A. M.	50	....	23	2.8	..	0.14	..	..	—	—	...	..	26	Carcinoma of stomach; treatment medical
36	A. K.	55	....	24	2.2	..	0.10	..	..	—	—	...	..	10	Carcinoma of stomach; necropsied
37	M. R.	40	....	26	2.3	..	0.11	..	..	—	—	...	..	18	Carcinoma of stomach; died after gastro-enterostomy
38	S. E.	58	5.7	27	2.6	..	0.10	..	..	—	—	...	..	14	Carcinoma of stomach; treatment medical
39	H. J.	77	....	30	2.4	..	....	..	..	+	—	120	60	..	Carcinoma of stomach; laparotomy; died
40	M. S.	59	6.7	30	2.7	..	0.14	..	..	+	++	118	75	14	Carcinoma of stomach; treatment medical
41	H. H.	42	6.5	36	2.8	..	0.14	..	..	—	—	100	64	6	Carcinoma of stomach; treatment medical
42	M. H.	35	3.0	37	2.4	..	0.11	..	..	—	—	..	..	3	Carcinoma of stomach; treatment medical
43	R. T.	50	....	40	3.5	..	0.13	..	..	+	—	..	..	29	Carcinoma of stomach; moderate anemia; died after operation
44	W. D.	37	5.3	43	2.0	..	0.13	73	Trace	++	++	...	..	10	Inoperable carcinoma of stomach; died following laparotomy
45	S. C.	60	....	47	...	..	....	..	..	+	+	...	..	21	Carcinoma of stomach; died after operation
46	R. C.	59	17.1	79	6.0	..	0.22	42	..	—	—	150	98	9	Inoperable carcinoma of stomach; died after laparotomy
47	J. H.	50	....	98	5.7	..	0.10	..	..	—	—	...	..	21	Carcinoma of stomach; died after laparotomy
48	J. D.	40	....	96	9.1	35	0.21	48	..	+	—	225	140	3	Carcinoma of stomach; pronounced anemia; arteriosclerotic fundi; 3 days later death uremic
				115	10.0	33	0.17	52	..						
49	C. S.	60	....	122	4.8	..	....	90	Trace	..	..	120	86	4	Carcinoma of stomach with metastases to liver; necropsied
50	C. G.	38	....	8	1.5	..	0.10	..	80	—	—	...	..	18	Carcinoma of transverse colon and gastro-hepatic omentum; laparotomy
51	N. W.	59	....	21	2.1	..	0.13	..	26	+	—	130	82	28	Carcinoma of descending colon; died following operation
52	W. W.	65	4.2	75	3.3	..	0.08	..	..	—	—	...	..	31	Carcinoma of cecum; died following operation
53	J. S.	47	7.5	27	3.6	..	0.11	..	..	—	-	...	..	14	Carcinoma of rectum; died following colostomy
54	E. G.	32	4.3	40	2.5	..	0.18	..	..	+	—	118	70	35	Carcinoma of rectum; died after radium therapy
55	J. F.	49	....	100	2.5	..	0.14	..	..	+	—	140	84	26	Carcinoma of rectum; blood specimen obtained after operation; death due to postoperative infection
56	S. T.	25	.. .	102	5.4	..	0.15	60	..	+	—	110	75	21	Carcinoma of rectum; improved after radium therapy
57	S. B.	63	2.7	12	1.9	..	0.13	51	62	—	—	...	..	10	Carcinoma of liver with metastases to stomach; laparotomy
58	A. P.	60	5.9	22	2.0	..	0.10	..	..	—	—	...	..	14	Carcinoma of liver with metastases to stomach; necropsied
59	P. L.	47	13.3	28	4.3	..	0.15	39	..	+	—	115	70	14	Carcinoma of liver; necropsied
60	D. M.	63	7.1	12	2.7	25	0.18	45	44	+++	+++	160	70	36	Carcinoma of pancreas; moderate anemia; necropsied
61	M. W.	44	....	13	1.9	22	0.20	60	..	++	—	...	..	7	Carcinoma of pancreas with metastases to liver; laparotomy
62	R. Z.	64	....	16	3.1	30	0.23	58	..	+	++	...	..	11	Carcinoma of head of pancreas involving duodenum; necropsied
63	J. J	67	....	30	...	20	0.17	..	..	+	—	120	60	21	Carcinoma of pancreas and gallbladder; laparotomy
64	B. S.	60	....	14	1.8	..	0.13	..	..	—	-	...	..	42	Retroperitoneal adenocarcinoma; laparotomy
65	J. F.	53	....	21	2.2	..	0.10	..	..	++	++	...	..	37	Retroperitoneal adenocarcinoma; laparotomy
66	E. R.	50	6.3	32	3.0	..	0.13	42	..	—	—	140	80	14	Retroperitoneal carcinoma; laparotomy
67	M. K.	66	6.7	53	3.7	..	0.20	39	..	—	—	120	70	5	Abdominal carcinomatosis; necropsied
68	T. G.	69	....	126	5.8	..	0.17	46	..	++	—	98	62	16	Abdominal carcinomatosis; died in uremia 6 weeks later

CHEMICAL CHANGES IN THE BLOOD COINCIDENT WITH MALIGNANT NEOPLASMS—(*Continued*)

No.	Case	Age	Blood Analyses						Phenolsulphonephthalein per Cent. in 2 Hrs.	Urine		Blood Pressure		Days Under Observation	Remarks
			Uric Acid	Urea N	Creatinin	Diastatic Activity	Sugar	CO_2 Combining Power		Protein	Casts	Systolic	Diastolic		
69	C. S.	54	4.4	11	2.4	..	0.11	65	..	—	—	...	..	14	Abdominal carcinomatosis; roentgen ray therapy; died
70	S. L.	41	....	28	2.1	..	0.18	..	..	—	—	...	..	29	General abdominal carcinomatosis; died following laparotomy
71	P. P.	51	....	37 102	4.4 11.2	..	0.12	.. 30	..	—	—	110	48	6	General abdominal carcinomatosis; death uremic
72	J. H.	40	9.7	58	3.3	..	....	..	..	++++	+++	...	..	6	General abdominal carcinomatosis; necropsied
73	J. F.	44	....	16	1.7	..	0.17	..	40	+	—	140	80	39	Carcinoma of left kidney with extensive metastasis; necropsied
74	J. B.	40	3.1	19	2.0	..	0.10	..	55	+	+	...	..	58	Sarcoma of left kidney; improved after nephrectomy
75	V. G.	44	....	54	6.0	..	0.12	..	Trace	++++	—	140	90	18	Hypernephroma; left hospital unimproved
76	W. L.	65	3.3	8	1.5	..	0.12	54	79	—	—	110	70	75	Carcinoma of bladder; improved after partial resection
77	J. B.	30	5.7	10 177	2.5 4.4	..	0.11	.. 41	20	— ..	— ..	... ...	.. ..	10 ..	Carcinoma of bladder 3 days after subtotal cystectomy; death uremic
78	J. K.	50	....	13	1.7	..	0.10	..	..	+	—	...	..	70	Carcinoma of bladder; death due to postoperative infection
79	E. P.	74	3.7 6.6	14 23	2.2 2.6	..	0.13	.. 50	Trace ..	++++ ..	— ..	... ...	.. ..	27 ..	Carcinoma of bladder 5 days after resection; uremic death 21 days later
80	P. L.	46	....	15 27 42	... ... 3.0	.. .. ..	0.11 0.13	.. .. ..	.. .. ..	+	—	... ...	.. .. ..	22	Malignant papilloma of bladder 19 days after resection Before death
81	L. W.	55	....	16	2.5	..	0.11	..	..	—	—	...	..	15	Recurrent carcinoma of bladder; improved after roentgen-ray therapy
82	S. G.	48	4.7	16 24 27	2.1 2.2 2.0	.. .. ..	0.12 0.15 0.14	 50	40	+	—	... ...	.. .. ..	34	Malignant papilloma of bladder 14 days after resection 19 days after resection; death
83	F. H.	54	5.7	19	2.0	..	0.10	..	27	+++	+	...	..	4	Carcinoma of bladder; died 4 days after excision of tumor
84	A. M.	50	....	23	2.8	..	0.13	..	..	—	—	...	..	11	Malignant papilloma of bladder; death due to postoperative infection
85	J. S.	40	....	24	2.0	..	0.09	..	Trace	++++	+	...	..	4	Carcinoma of bladder; died after resection
86	P. V.	60	....	39 49	5.3 5.0	.. ..	0.15 0.10	.. 40	..	++++ ..	— ..	... ...	.. ..	14 ..	Carcinoma of bladder After cystotomy; died 9 days later
87	E. H.	39	....	42	3.5	..	0.15	40	..	++++	—	...	..	14	Carcinoma of bladder; died following cystotomy
88	J. G.	32	6.0	45	3.6	..	0.12	..	7	+	—	140	80	5	Carcinoma of bladder; died following resection
89	W. F.	66	....	53	4.5	..	0.09	..	..	+	—	...	..	10	Carcinoma of bladder; died following resection
90	J. R.	69	....	53 29 50	5.0 2.5 3.8	.. .. ..	0.12 0.12 0.13	.. 50 ..	..	+	—	135 170 ...	80 110 ..	40	Carcinoma of bladder After cystotomy 13 days after cystotomy; patient died 2 months later
91	F. C.	57	7.6	56	4.5	..	0.12	43	..	+	—	...	..	2	Carcinoma of bladder; died following resection

92	E. K.	45	14.9	58	8.0	..	0.18	..	12	++	—	...	..	30	Carcinoma of bladder; uremic death after resection
93	O. P.	59	....	125	6.8	24	0.18	32	..	++	—	...	..	34	Carcinoma of bladder; cystotomy 3 months previous; uremic death
94	H. C.	59	....	169	6.0	25	0.21	40	Trace	—	—	...	..	19	Carcinoma of bladder; died after resection
95	I. L.	65	2.9	13	2.3	..	0.14	..	..	++++	—	...	..	30	Carcinoma of prostate; improved after prostatectomy
96	M. W.	56	5.2	13	2.5	..	0.15	..	..	+	—	...	..	11	Carcinoma of prostate
				76	5.1	..	0.25	42	..	..	..	...	..	..	9 days after prostatectomy; died 2 days later
97	C. L.	75	4.2	14	1.8	..	0.12	..	48	+++	—	...	..	74	Carcinoma of prostate
			7.5	59	4.8	..	0.18	..	..	..	..	...	..	..	6 days after prostatectomy; died
98	M. I.	75	....	14	1.7	..	0.09	..	33	+	+	...	..	30	Carcinoma of prostate; died in coma following prostatectomy
				147	5.7		0.19	40							
99	H. K.	67	....	17	2.3	..	0.13	..	..	—	—	...	..	11	Carcinoma of prostate; died from post-operative infection
100	J. D.	59	....	18	1.5	..	0.12	..	..	—	—	120	80	14	Carcinoma of prostate; radium therapy
101	W. H.	73	....	20	2.1	..	0.12	..	..	+	—	...	..	29	Carcinoma of prostate; improved after prostatectomy
102	W. P.	69	....	21	2.5	..	0.11	..	..	+	—	...	..	20	Carcinoma of prostate; died following perineal prostatectomy
103	S. B.	69	....	22	2.4	.	0.13	43	20	+	—	...	..	11	Carcinoma of prostate; not operated; unimproved
104	J. S.	62	.. .	22	...	..	0.18	..	..	+	—	...	..	9	Carcinoma of prostate; died after prostatectomy
105	J. M.	68	....	23	2.9	..	0.11	..	..	+	—	...	..	48	Carcinoma of prostate; improved after prostatectomy
106	P. M.	66	....	24	2.2	..	0.13	58	11	++	—	...	..	22	Carcinoma of prostate; died after prostatectomy
				45	3.2		0.14	38							
107	C. T.	55	....	24	2.6	..	0.18	32	..	+	—	...	..	43	Carcinoma of prostate; died after prostatectomy
108	C. P.	58	....	25	3.5	..	0.14	41	Trace	+	—	...	..	30	Carcinoma of prostate
				74	...	..	....	24	..	..	..	...	..	..	4 days after operation; death uremic
109	W. K.	69	7.5	42	2.6	..	0.12	34	..	+	—	...	..	6	Carcinoma of prostate; not operated; died in coma
110	A. D.	49	....	43	4.4	..	0.12	..	..	—	—	...	..	3	Carcinoma of prostate; not operated; unimproved
111	S. K.	58	7.7	44	4.6	..	0.13	28	Trace	++	—	...	..	5	Carcinoma of prostate; died after prostatectomy
112	H. M.	69	5.6	46	4.1	..	0.13	..	..	..	..	180	91	12	Carcinoma of prostate; not operated; unimproved
113	R. J.	70	7.0	52	4.4	..	0.15	33	..	++++	—	...	..	6	Carcinoma of prostate
				75	6.2	..	0.17	41	..	..	.	...	..	..	After alkali therapy; not operated; died
				102	6.0		0.15								
114	P. W.	46	....	15	2.3	.	0.10	47	47	+	—	...	..	42	Carcinoma of penis
				31	2.9	..	0.10	..	..	..	..	...	..	..	10 days after amputation; generally improved
115	M. M.	47	5.0	14	2.6	..	0.14	..	57	—	—	...	..	20	Sarcoma of uterus; improved after hysterectomy
116	C. C.	38	....	32	4.0	..	....	..	..	—	—	...	..	10	Carcinoma of cervix of uterus; died after hysterectomy
117	A. R.	56	10.0	49	13.0	..	0.16	..	..	+	—	145	80	90	Carcinoma of uterus; marked anemia
			11.7	107	20.0	.	0.14	38	..	..	..	...	..	..	10 days later, after transfusion; not operated; died in coma
118	A. D.	53	....	198	14.4	..	0.15	27	Trace	+	+	180	105	16	Carcinoma of uterus; Wassermann ++++
			8.3	99	16.5	..	0.17	..	..	..	..	140	90	..	After 8 days rest and dietetic restrictions
				114	19.8	..	0.18	76	..	..	..	...	..	..	After 12 days of alkali therapy; died 2 days later in uremia
119	M. W.	40	10.6	151	21.0	..	0.21	53	..	++	++	120	90	11	Carcinoma of cervix of uterus; on alkali and radium therapy; died 10 days after blood examination

DISCUSSION

The results of studies on chemical changes in the blood on 119 cases of various types of malignancies are presented in the table. It will be observed on inspection of these findings that in three cases only (Cases 3, 57, 95) the uric acid concentration of the blood was less than 3 mg. per 100 c.c. In the other cases, however, it ranged from 3.3 to 17 mg., the majority of the figures being above 5 mg. Myers [13] and his co-workers have frequently pointed out that the uric acid concentration of normal blood is from 2 to 3 mg. per 100 c.c., but as the permeability of the kidney is lowered in the initial stages of renal impairment, this is first indicated in the analysis of the blood by an increase of the concentration of uric acid. This failure to excrete the uric acid is a more reliable and an earlier indication of an insufficiency of kidney function than a proteinuria or cylindruria. Later, as the involvement of renal function progresses, the urea accumulates in the blood, but, in general, there is no perceptible rise in the creatinin concentration until the urea nitrogen has doubled or more than doubled. It is evident that this order of retention of the nitrogenous waste products must depend on the comparative ease with which the kidney excretes them. Myers and Fine [14] have pointed out that the kidney normally concentrates the creatinin 100 times, the urea eighty times, but the uric acid only twenty times. Hence, of these compounds the creatinin is the most readily and the uric acid the most difficultly eliminated, with the urea standing in an intermediate position. After a thorough study of tests of renal function in a large series of cases, Baumann, Hansman, Davis and Stevens [15] have concluded that the rise in the uric acid concentration of the blood is the most sensitive index of a failing kidney function at our disposal. It will be noted that in many instances (Cases 1, 60, 77, 79, 83, 97) the high uric acid figures are associated with a definite decrease in the phenolsulphonephthalein excretion although normal values for urea nitrogen and creatinin are reported. This increased concentration of the uric acid in the blood must, then, be attributed to a beginning impairment of renal function.

The urea nitrogen content of normal blood has been placed by Kast and Wardell [16] between 12 and 15 mg. per 100 c.c., and Folin [17]

13. Myers, Fine and Lough: Arch. Int. Med. **17**:570 (May) 1916; Chace and Myers: J. A. M. A. **67**:929 (Sept. 23) 1916; Myers and Fine: Chemical Composition of Blood in Health and Disease, New York, 1915.

14. Myers and Fine: J. Biol. Chem. **37**:239, 1919.

15. Bauman, Hansman, Davis and Stevens: Arch. Int. Med. **24**:70 (July) 1919.

16. Kast and Wardell: Arch. Int. Med. **22**:581 (Oct.) 1918.

17. Folin: J. A. M. A. **69**:1209 (Oct. 13) 1917.

has stated that the maximum concentration of this component in normal blood is from 14 to 15 mg. per 100 c.c. It has been shown by Mosenthal and Lewis [18] and by others that in the secondary disturbance of kidney function due to irritation there first develops a stage of renal hyperactivity in which a very rapid elimination of urea and an excessive output of phenolsulphonephthalein are noted. The increased excretion of the urea leads to a decreased concentration of this product in the blood. Four cases in the table (Cases 16, 30, 50, 76) show subnormal values for the urea nitrogen from 8 to 11 mg. per 100 c.c., and uric acid figures within normal limits. These findings are similar to many reported by Theis and Stone, but we believe the decreased urea nitrogen of the blood is due, not to any excessive demand for nitrogen by the new growth, but rather to a hyperpermeability of the kidney for the nitrogenous waste products. The fact that these low figures for urea nitrogen are associated with an increased output of phenolsulphonephthalein (from 60 to 85 per cent.) lends support to our opinion. These cases apparently represent instances of renal hyperpermeability in a kidney involvement probably due to a toxemia, and analogous to conditions described by Mosenthal and Lewis.

A study of Cases 77, 79, 82, 96, 97 is particularly instructive. In these instances high figures for uric acid but normal values for urea nitrogen were obtained in the first analyses of the blood, but after an aggravation of the kidney involvement due to surgical interference, there is noted a marked increase in the urea nitrogen and a beginning retention of the creatinin. An increase in the urea nitrogen of the blood to 20 mg. or more is considered by Kast and Wardell to have a pathological significance. Figures for urea nitrogen exceeding 20 are found particularly in malignancies of the viscera. In the majority of external tumors and in about 50 per cent. of the cases of carcinoma of the stomach normal values for this factor have been obtained.

It is evident from the studies of Myers and Killian [19] that the blood creatinin furnishes a better prognostic insight into the extent of the involvement of kidney function than either the urea of the blood or the phenolsulphonephthalein test. For normal individuals the creatinin of the blood amounts to from 1 to 2 mg. per 100 c.c. Figures of 3 mg. or more are, with but few exceptions, accompanied by a marked urea retention, and although many patients with a creatinin concentration of 4 mg. or less have shown improvement under treatment, cases with more than 4.5 or 5 mg. almost invariably

18. Mosenthal and Lewis: J. A. M. A. **67**:933 (Sept. 23) 1916.
19. Myers and Killian: Am. J. M. Sc. **157**:674, 1919.

terminate fatally. In the series reported here, an increase in the creatinin content of the blood is found in those cases in which the retention of urea has already reached a high level. In many instances the damage to kidney function has been sufficient to produce an accumulation of creatinin of 4 mg. or more. The termination of many of these cases was typically uremic.

Since the development of malignant neoplasms in the human organism almost invariably produces a more or less severe anemia, this must be considered as a possible factor modifying the composition of the blood. While Mosenthal and Lewis noted a range of urea nitrogen in five cases of anemia, primary and secondary, from 6 to 14 mg., Tileston and Comfort's [20] cases of severe anemia due to hemolysis were characterized by a marked retention of nonprotein and urea nitrogen. Gettler and Lindeman [21] recently reported in pernicious anemia a significant rise in the uric acid. The nonprotein and urea nitrogen and creatinin, though less markedly increased, were, in general, above normal. A decrease in the amount of circulating blood rather than an impairment of renal function was suggested as a cause of these abnormal values. If this were true, the increase in concentration would have been proportionately the same for all three compounds.

Bock [22] has determined the total blood volume and the blood plasma volume by the vital red method in a series of thirty cases representing extremes of total corpuscle content, and wide range of total blood volumes. He has found that the blood plasma volume is very constant, forming on the average of 5.1 per cent. of body weight. Variations in the total blood volume per kilogram of body weight are due to changes in the corpuscular content of the blood.

Denny [23] has utilized the changes in the oxygen capacity of the recipient's blood produced by a transfusion of a definite amount of donor's blood of known oxygen capacity, to calculate the total blood volume and the blood plasma volume in ten cases of pernicious anemia. This author has shown that although the total blood volume was decreased in all but two cases, the blood plasma volume remains essentially normal, the decrease in total volume being due to a loss of cell mass. The decrease in the enumeration of blood cells in the cases studied by Bock and Denny are more pronounced than any noted in our series. The maximum decrease in blood volume in these cases would produce at most an increase in the concentration of nonprotein

20. Tileston and Comfort: Arch. Int. Med. **14**:620 (Nov.) 1914.
21. Gettler and Lindeman: Arch. Int. Med. **26**:453 (Oct.) 1920.
22. Bock: Arch. Int. Med. **27**:83 (Jan.) 1921.
23. Denny: Arch. Int. Med. **27**:38 (Jan.) 1921.

nitrogenous constituents of but 1.2 times. It is apparent, then, that the diminished blood volume cannot account for the marked rise in the nonprotein nitrogenous constituents noted by us. Moreover, we find that all three of the nitrogenous waste products are not increased to the same extent. On the contrary, a definite order of retention has been demonstrated—the first product to be retained is the uric acid, next the urea and finally the creatinin. It is inconceivable that a diminished blood volume could produce a subnormal excretion of phenolsulphonephthalein, even before an accumulation of urea or creatinin had taken place. When the anemia secondary to the malignancy in our cases has been moderate or severe, this has been noted under remarks. There is no apparent relation between the changes observed in the composition of the blood and the anemia associated with the malignant neoplasms.

With the exception of the carcinomas of the pancreas, a hyperglycemia and an increased diastatic activity of the blood, indicating a lowered tolerance for carbohydrate, were encountered only in those cases manifesting a nitrogen retention. As this retention became more marked, the hyperglycemia, and the increased diastatic activity kept pace with it. Apparently then, the hyperglycemia noted by Benedict and Lewis, Trinkler and Cammidge and the increased diastatic activity reported by De Niord and Schreiner must be attributed, not specifically to the malignant new growth but rather to the impairment of renal function. It is well known that many cases of severe nephritis with nitrogen retention give high figures for blood sugar. Myers and Killian [24] have reported an increased diastatic activity of the blood and a hyperglycemia in advanced nephritis, and Williams and Humphreys [25] state that the level of the blood sugar in nephritis depends upon the severity of the renal insufficiency.

The tolerance for glucose in nephritis has been carefully studied by Hamman and Hirschman [26] who have obtained blood sugar curves after the ingestion of glucose closely resembling diabetic curves. The disturbance of renal function raises the threshold for sugar excretion so that a marked hyperglycemia may result without a glycosuria. An interesting case has been described by Bailey,[27] in which the blood sugar rose to 0.30 per cent. before traces of sugar could be detected in the urine. The high blood sugar curves persisting after the ingestion of 100 gm. glucose by cancerous patients described by Rohdenburg, Bernhard and Krehbiel and by Friedenwald and Grove, and considered by

24. Myers and Killian: J. Biol. Chem. **29**:179, 1917.
25. Williams and Humphreys: Arch. Int. Med. **23**:537 (May) 1919.
26. Hamman and Hirschman: Arch. Int. Med. **20**:761 (Dec.) 1917.
27. Bailey: Arch. Int. Med. **23**:455 (May) 1919.

these authors to be characteristic of malignancy, find an explanation in this disturbance of renal function. Further evidence in support of this explanation is furnished by the absence of a glycosuria in spite of a pronounced hyperglycemia (from 0.24 to 0.30 per cent.).

Four cases of carcinoma of the pancreas (Cases 60, 61, 62 and 63) have been studied by us. In two cases the diagnosis was confirmed by necropsy, and in the other two by operation. In all instances a hyperglycemia (from 0.17 to 0.23 per cent.) and a definitely increased diastatic activity (from 20 to 30 per cent.) were found. In one case there was a retention of uric acid alone, and in another an increased urea nitrogen, but the impairment of kidney function here was not sufficient to account for the hyperglycemia and increased diastatic activity. In all cases there was noted a glycosuria. This increased diastatic activity of the blood, the hyperglycemia and the glycosuria, we believe, are of some diagnostic value in malignancies involving the functions of the pancreas.

According to Van Slyke and his collaborators[28] normal blood plasma has a carbon dioxid binding capacity of from 53 to 77 volumes per cent. A study of the figures in the table for the carbon dioxid combining power of the blood plasma reveals a normal or slightly decreased alkali reserve of the blood in the cases of malignancy without a retention of nitrogen. We have found no evidence of an increased basicity reported by Moore and Wilson, and Menten. In Case 49 a carbon dioxid combining power of 90 was found, with a severe retention of urea and creatinin. Here, however, a diagnosis of gastric ulcer had originally been made and huge doses of sodium bicarbonate had been administered by mouth daily for a period of fourteen days previous to admission to the hospital. This alkali therapy undoubtedly was responsible for the abnormal carbon dioxid combining power of the blood. A definite decrease in the reserve alkali of the blood plasma indicating a moderate or severe acidosis is found in many cases showing nitrogen retention. A ketosis, however, was uniformly absent. There appears to be a causal relation between the severity of the kidney impairment and the acidosis noted and no doubt, the mechanism of production of this acidosis is analogous to that causing the acidosis in nephritis. Chace and Myers[29] have found in cases of severe nephritis an associated acidosis, sufficient in many instances to be the actual cause of death.

These observed changes in the blood cannot be explained by a nephritis independent of the malignancy, to be expected in patients of advanced age. The degree of renal impairment bears no relation

28. Stillman, Van Slyke, Cullen and Fitz: J. Biol. Chem. **30**:405, 1917.
29. Chace and Myers: J. A. M. A. **74**:641 (March 6) 1920.

to the age of the patients. In fact, the most pronounced retention of urea nitrogen and of creatinin observed was in a case of a woman, aged 25 years. The systolic and diastolic blood pressures are in general normal or subnormal. A hypertension was noted in but one case, where there was other evidence of general arteriosclerosis. An examination of the ocular fundi revealed normal pictures in all cases with the single exception of this arteriosclerotic (Case 48). Although proteinuria was frequently encountered, the amount of protein excreted in the urine was not a reliable index of the kidney impairment. Casts were rarely seen.

The accumulation of these nitrogenous waste products cannot be ascribed to an increased metabolism produced by the growth of the tumor within the organism, inasmuch as the removal of the neoplasm does not decrease the concentration of these nitrogenous substances. On the contrary in many instances the nitrogen retention after the operation greatly exceeds the preoperative findings.

Turning to the more practical side of this question, it is obvious that since malignant tumors in the human organism in many instances entail a secondary impairment of renal function, an examination of the kidney activity should be made as a preoperative measure. It has been our experience that frequently anesthesia and surgical interference have provoked an acute exacerbation of the renal involvement with a fatal termination. The aggravation of the kidney damage after operation is not dependent on a postoperative infection, for the effect of the surgical procedure upon the renal function appears too rapidly after operation to be due to infection. Furthermore, in three cases death was due to postoperative infection, but in two of these cases following operation there was no increase in nitrogen retention. In the third case the specimen of blood examined was obtained ten days after operation and the retention of nitrogen found may be due to a kidney involvement secondary to *B. welchii* infection. It is obvious that a chemical examination of the blood will afford the surgeon more accurate and reliable information concerning the functional capacity of the kidneys than a urinalysis. Squier and Myers [30] have emphasized the preoperative prognostic value of the blood urea in surgery on the prostate, and we believe their conclusions are tenable also in malignancies. Patients showing urea nitrogen figures under 20 mg. per 100 c.c. may be regarded as good operative risks so far as the kidney activity is concerned, but when the urea nitrogen rises to 20 or 30 mg. the patient should be operated on with great caution, and a retention to 30 mg. or more indicates a poor operative risk. However, it is our opinion that patients showing an increase in the uric acid only with a

30. Squier and Myers: J. Urol. **2**:1, 1918.

subnormal phenolsulphonephthalein excretion, as Cases 77, 79, 82, 83, should not be operated on except in extreme emergency, until preliminary treatment has brought the kidney function up to normal standards. Since Killian [31] and Short [32] have reported a decrease in the alkali reserve of the blood after general anesthesia and surgical procedures, a preoperative examination of the carbon dioxid combining power of the blood in these cases, particularly where a nitrogen retention has been found, will indicate to the surgeon the necessity of guarding against a postoperative acidosis.

SUMMARY

Of the 119 cases of malignancy examined, about 80 per cent. show a definite increase in the uric acid concentration of the blood, and about 60 per cent. an increase of the urea nitrogen and creatinin, indicating a more or less severe impairment of kidney function. The appearance and progress of this renal insufficiency follows the order of retention of the nitrogenous waste products characteristic of nephritis of the interstitial type. This impairment of renal function was found invariably in general abdominal carcinomatosis, in about 90 per cent. of cases of carcinoma of the bladder, prostate, uterus and rectum, in about 50 per cent. of cases of carcinomas of the stomach, and rarely in external tumors. In all cases of nonmalignant tumors no such disturbance of kidney function has been noted. The accumulation of the nitrogenous waste products in the blood was paralleled by a decrease in phenolsulphonephthalein excretion, but many of the other signs indicative of nephritis, e. g., hypertension and changes in the ocular fundi, were lacking. The extent of the renal insufficiency was independent of the age of the patients and the associated anemia. Disturbances of carbohydrate tolerance were found to be dependent on the kidney involvement rather than on the malignancy itself. An acidosis was encountered in many instances, particularly in cases showing nitrogen retention. A pre-operative chemical examination of the blood is of great prognostic value in malignancy, since it serves as an excellent index of renal function and also of any acidosis.

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31. Killian: Proc. Soc. Exper. Biol. and Med. **15**:17, 1917.
32. Short: J. Biol. Chem. **41**:503, 1920.

A STUDY OF THE UREA CONCENTRATION TEST FOR KIDNEY FUNCTION *

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MONTREAL

Advances made in recent years in laboratory methods for the study of kidney function have extended our interests beyond the observation of structural changes. The finding of albumin, casts, blood or pus in the urine, is in the great majority of cases definite evidence of structural changes in the kidney. Newer laboratory methods have, however, taught us that anatomic and functional integrity of the kidneys are not synonymous terms. Serious functional changes may be found clinically, and at necropsy no commensurate degree of tissue destruction may be noted. Extensive tissue destruction may be found at necropsy, and with our present methods of determining functional activity, no marked impairment may be found clinically. Much is still unknown regarding the physiology of the kidney. For this reason any new method devised as a means of determining kidney function is welcomed by the clinician.

In February, 1920, MacLean and de Wesselow [1] reported a method for determining kidney function, which they called the "new urea concentration test." These authors found "that when a large dose of urea was administered to a patient with defective kidneys, the patient was incapable of excreting urine with a high urea concentration." The test appeared to be a quantitative one. From their findings they concluded that in their experience it was of more value in indicating deficiency of kidney function than other tests then (1920) in use.

Details of the test as described by its authors are as follows: "The patient empties his bladder and immediately afterward takes 15 gm. urea dissolved in 100 c. c. water. One hour after taking the urea, he passes water. This sample is kept for estimation of urea percentage. Two hours after administration of the urea he again passes water. This sample is also kept for estimation of urea percentage."

The urea was estimated by the hypobromite method. Any concentration over 2 per cent. was taken as an index of fair efficiency; below 2 per cent. was considered unsatisfactory, and the lower the concentration the more serious the lesion. The value of the method

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1. MacLean, H., and de Wesselow, O. L. V.: On the Testing of Renal Efficiency, with Observations on the Urea Coefficient, Brit. J. Exper. Path. **1**:53 (Feb.) 1920.

as a quantitative test was emphasized, and they criticized the "urea coefficient test" (MacLean Index) which they regarded as a qualitative test only and in the presence of a normal blood urea it "is only a waste of time and labor to utilize a complicated mathematical formula, when the same information can be obtained from the urea concentration alone."

While attempting to compare this method with other methods employed in the routine of examination of kidney function in the Montreal General Hospital, an opportunity was afforded, at the same time, of reviewing the work done on kidney function during the last year. Practically every well known method has been given consideration. Eventually, a routine has been adopted which seems, in our experience, to be practical and to give the desired information. Up to the present, the minimum investigation carried out in all cases admitted to the wards, which were found to have an albuminuria, consisted of the estimation of the blood urea, blood creatinin, and of the percentage excretion of phenolsulphonephthalein in two hours.

Table 1 shows the general routine followed.

TABLE 1.—ROUTINE ADOPTED FOR ESTIMATING KIDNEY FUNCTION

Clinical Condition	Examination									
	NPN	BU	BCr	UrAc	NCl	PST	RTM	NU	AUT	DIO
Hypertension	+	+	+	+	+	+	+			
Suspected early nephritis	+	+	+	+	+	+	+			
Acute nephritis	.	+	+	..	+	+	..	+	+	+
All edemas	..	+	+	..	+	+	..	+	+	
Surgical kidneys (preoperative)	..	+	+	..	..	+	..	+	+	
Prostatic enlargement (preoperative)	+	+	+	..	..	+	+	+	+	
Cardiac cases (for diagnosis)	+	+	+	..	+	+	+	..	+	
Cardiac cases (for progress)	..	+	..	..	+	+	..	+	..	+

Explanation of abbreviations: NPN, nonprotein nitrogen of the blood; BU, blood urea; BCr, blood cratinin; UrAc, blood uric acid; NCl, Actual, calculated and threshold of blood chlorids; PST, phenolsulphonephthalein; RM, Mosenthal renal test meal; NU, night urine; AUT, urea concentration test (MacLean and de Wesselow); DIO, daily intake and output of fluids.

Judging from our experience, with this routine laboratory procedure, we cannot help but conclude that there is no one single test for kidney function, which, employed to the exclusion of all others, has not its limited sphere of usefulness. It may reveal a fraction of the cause of the clinical symptoms, and a very valuable one, but at its best, it is only a laboratory aid, and must be correlated with the clinical picture in order to reach a final diagnosis, which latter has justly been called "a complex clinical judgment." The reason for this seems quite obvious. The study of a pathologic reaction is the study of a disturbed physiologic reaction, and the exact physiology of the kidney is still obscure.

A careful study was made of this new "urea concentration test" to determine its value as compared with the routine methods now in use. No choice was made of the cases clinically. These were studied as they were admitted to the wards, and included marked cardiac, cardiorenal, marked renal cases, and those cases admitted for other clinical pictures but which were also found to have an albuminuria.

Table 2 presents a list of the first fifty cases studied. Since the same conclusion could be drawn from the study of subsequent analyses, further tabulation seemed unessential.

In all the determinations of the urea in the blood and urine, the very accurate method of Van Slyke was employed.

The minimum information obtained in each case consisted of the percentage of blood urea, blood creatinin, percentage of phenolsulphonephthalein excretion in two hours, and the urea concentration test. Wherever it was clinically possible a complete Mosenthal renal test meal was done. In nearly every case the character of the night urine was studied. This was done by allowing the patient a full hospital diet. No food nor fluids were allowed after the evening meal. At 8 p. m. sharp the patient voided urine. This specimen was discarded. All subsequent specimen were collected until 8 a. m. the following day. This twelve hour specimen was examined for volume and concentration of nitrogen. We have termed this the "nocturnal urine test." No originality is claimed for this test. Mosenthal in his original description [2] of his modification of the Hedinger and Schlayer meal pointed out that it was unnecessary to adhere exactly to the details of the meal when no balance determination was required, and Christian, in describing his modification of the meal,[3] again emphasized this point.

In each case the clinical picture was studied as completely as possible, and an attempt was made to correlate this with the functional findings.

In interpreting our observations, a few theoretic considerations seem essential. Since the test centers about the excretion of urea a little consideration of the physiology of this product is necessary.

Urea is the chief nonprotein nitrogenous element found in the urine. On an ordinary diet, in a normal person, its nitrogen content may be as much as from 80 to 90 per cent. of the total nitrogen excreted during the day. From this consideration alone it appears that this new test might be similar to one already in use, and duplication of work must be avoided in a large general hospital with a large routine. In describing

2. Mosenthal, H. O.: Renal Function as Measured by the Elimination of Fluids, Salt and Nitrogen, and the Specific Gravity of the Urine, Arch. Int. Med. **16**:733 (Nov.) 1915.

3. Christian, H. A.: The Use of Tests of Renal Function in Cases of Nephritis, J. Urol. **1**:319, 1917.

TABLE 2.—Cases Arranged According to their Degree of Concentration of Blood Urea

No.	Hospital No.	Blood, Mg. per 100 C.c.			Urine					Clinical Remarks
					Urea Concentration, per Cent.		Night Urine		Phenolsulphonephthalein per Cent. in 2 Hours	
		Urea N Before	Urea N After	Creatinin	1st Hour	2d Hour	C.c.	Per Cent. N		
1	1066	11	17	1.20	1.74	2.02	580	0.802	58	Chronic interstitial nephritis
2	1411	12	25	1.75	1.76	2.13	510	0.696	55	Chronic interstitial nephritis
3	1254	13	30	1.59	2.25	2.04	430	0.896	41	Cardiorenal; edema
4	1573	14	30	1.10	2.59	....	310	1.260	32	Chronic nephritis; pregnancy
5	1595	15	25	1.75	1.92	1.86	720	0.644	60	Rheumatoid arthritis; albuminuria
6	1498	16	32	1.40	1.20	1.26	600	0.840	..	Perineal fistula; albuminuria
7	1557	16	33	1.30	1.32	0.96	500	0.560	45	Acute nephritis
8	1896	16	30	1.59	3.0	3.00	220	2.100	55	Acute nephritis; erysipelas
9	1783	17	26	1.40	1.63	1.49	540	1.17	38	Prostatic hypertrophy; chronic nephritis
10	X	17	26	2.0	0.66	0.72	560	0.410	32	Hypertension; chr. nephritis
11	1540	18	35	1.59	1.80	1.86	580	0.656	42	Prostatic hypertrophy; chronic nephritis
12	1737	20	35	1.40	2.56	2.91	125	2.20	58	Sarcoma; albuminuria
13	1045	21	28	1.61	1.36	2.43	320	1.40	62	Malaria; albuminuria
14	1605	21	32	1.91	1.80	1.80	580	0.621	21	Puerperal septicemia
15	1647	21	30	1.80	1.70	1.78	600	0.105	52	Chronic interstitial nephritis
16	1680	21	35	1.30	2.42	....	425	0.921	50	Early interstitial nephritis
17	1772	21	26	1.00	2.59	2.76	220	1.00	76	Turpentine poisoning; chronic nephritis
18	1836	21	30	1.90	1.72	....	500	0.920	44	Chronic interstitial nephritis
19	X	21	38	1.75	2.34	2.76	570	0.760	..	Acute pancreatitis; albuminuria
20	X	23	..	1.40	4.04	3.36	102	1.360	46	Acute nephritis; empyema
21	2015	21	39	1.08	2.36	....	250	1.26	..	Cardiac; albuminuria
22	2015	19	..	1.57	2.07	2.28	250	1.70	45	Carcinoma; chronic nephritis
23	2014	16	26	2.10	0.73	1.68	450	0.682	42	Acute nephritis
24	2089	19	32	1.15	2.46	2.73	260	1.96	62	Chronic tuberculosis; albuminuria
25	1452	24	35	1.80	1.87	1.92	600	0.346	31	Prostatic hypertrophy; chronic nephritis
26	1505	25	..	1.50	1.44	1.51	600	0.300	22	Cardiac; passive congestion
27	1702	25	36	1.75	3.00	3.00	430	0.840	58	Pericarditis; albuminuria
28	1686	26	46	....	3.00	3.00	235	1.730	38	Passive congestion
29	5535	28	..	1.90	1.38	....	760	0.462	30	Prostatic hypertrophy; chronic nephritis
30	1921	28	42	2.00	2.13	1.44	540	0.620	52	Acute nephritis
31	1540	28	51	1.50	2.22	2.56	520	0.640	41	Prostatic hypertrophy; chronic nephritis
32	1896	31	43	1.40	1.90	1.90	560	0.421	27	Advanced cardiac; chronic nephritis
33	1788	32	49	1.75	1.56	1.56	700	0.780	Trace	Advanced cardiac; chronic nephritis
34	1744	32	42	1.80	1.44	1.40	520	0.588	47	Chronic nephritis
35	1172	32	43	1.61	1.92	2.64	400	1.35	55	Myxedema; albuminuria
36	1577	29	41	1.75	2.22	1.62	425	0.09	45	Fracture of femur; albuminuria
37	1690	32	35	2.00	2.79	2.79	540	0.840	50	Pneumonia; acute nephritis

TABLE 2.—Cases Arranged According to their Degree of Concentration of Blood Urea—(*Continued*)

No.	Hospital No.	Blood, Mg. per 100 C.c.			Urine					Clinical Remarks
					Urea Concentration, per Cent.		Night Urine		Phenolsulphonephthalein per Cent. in 2 Hours	
		Urea N Before	Urea N After	Creatinin	1st Hour	2d Hour	C.c.	Per Cent. N		
38	1300	32	47	1.70	1.26	1.64	600	0.360	26	Prostatic; arteriosclerosis
39	1922	34	45	2.40	1.92	2.25	640	0.561	54	Prostatic; chronic nephritis
40	1874	34	46	2.30	1.35	1.32	540	0.520	15	Hypertension; arteriosclerosis
41	1749	35	43	1.75	1.25	0.95	480	1.130	50	Chronic interstitial nephritis
42	1639	35	42	1.66	2.25	2.64	560	1.103	..	Prostatic; chronic nephritis
43	1676	34	45	2.20	2.10	2.00	500	0.780	55	Prostatic; chronic nephritis
44	1429	35	46	....	2.30	2.42	600	0.320	41	Chronic lead poisoning; chronic nephritis
45	1451	31	..	2.13	2.66	2.43	600	0.620	39	Chronic interstitial nephritis
46	1427	49	..	1.66	3.10	3.30	580	0.820	36	Hernia; chronic nephritis
47	2011	49	58	1.66	2.76	2.91	640	0.820	45	Chronic interstitial nephritis
48	2103	35	..	1.76	1.50	1.74	660	0.320	37	Advanced cardiorenal
49	1916	60	67	3.00	1.78	1.80	...	0.860	Trace	Advanced chronic nephritis
50	1703	132	140	8.75	1.20	0.84	760	0.220	Trace	Advanced chronic uremic

the renal test meal Mosenthal has shown[2] that the normal kidney is able to excrete urine with a nitrogen concentration of over 1 per cent. Since normally from 80 to 90 per cent. of the total nitrogen is excreted as urea, to state that any concentration of over 2 per cent. urea is an index of fair efficiency, seems to be a restatement of Mosenthal's finding that a concentration of over 1 per cent. nitrogen is normal. This becomes quite apparent on an analysis of the chemical formula for urea, $C{=}O{<}^{NH_2}_{NH_2}$. It will be observed that for each sixty parts of urea there are twenty-eight parts of nitrogen. That is, 2.14 times the nitrogen equals the urea. That this actually is the case seems well borne out on analysis of Table 3. Every case showing a low urea concentration test, also showed a low concentration of nitrogen (under 1 per cent.) in the night urine. Incidentally, nearly every case showing either a low nitrogen concentration or low urea concentration also showed a polyuria (over 400 c.c.). This nocturnal polyuria has long been known clinically as evidence of impairment of kidney function. Although in the great majority of cases the administration of urea by mouth did not inconvenience the patients, occasionally vomiting or nausea did follow. This must necessarily be avoided in acutely ill cases. The determination of the character

of the night urine does not in any way whatever interfere with the patient, and from its consideration so far its results parallel those of "the urea concentration test."

Another factor to be considered is the rate of absorption of urea from the alimentary tract. In any test involving the administration of substances by mouth this becomes an important factor. Allen [4] has pointed out the varying results obtained when equal amounts of sugar are given by mouth, subcutaneously or intravenously. Recently in a study of nitrogen elimination McEllroy and Pollock [5] have shown that the rate of elimination of nitrogen is an index of the rate of absorption. That this factor of absorption plays an important part in the results obtained in the "urea concentration test" seems apparent, from a study of Table 3 and after certain physiologic phenomena are considered. Marshall and David [6] have shown that urea is evenly distributed throughout the tissues of the body in the same concentration as in the blood. It has been assumed [7] that for each kilogram of body weight there are about 700 c.c. of fluid. This has been later shown to be remarkably accurate.[8] If, then, we accept this figure as correct, the administration of 15 gm. urea (7 gm. nitrogen) by mouth to a patient weighing about 60 kg. (taking for granted that urea is readily soluble, and undergoes no chemical alteration in the body, and is evenly distributed) should raise the concentration of urea nitrogen in the blood about 16 mg. per 100 c.c. Table 3 shows the effect of the oral administration of 15 gm. urea on the blood:

TABLE 3.—Effect on Blood of Ingestion of 15 Gm. Urea

Time of Test	Blood Urea N, Mg. per 100 C.c.
Before administering urea	19.2
10 minutes after administering urea	22.1
20 minutes after administering urea	23.6
30 minutes after administering urea	22.1
40 minutes after administering urea	20.2
50 minutes after administering urea	21.0

At the end of this fifty-minute period the patient voided 160 c.c. urine with a urea concentration of 3.1 per cent. That is, 4.96 gm. urea were excreted. Reconsidering the previous mathematical observations, some disturbance in the absorption seems to have

4. Allen, F. M.: Glycosuria and Diabetes, Harvard Univ. Press, 1913.

5. McEllroy, W. S., and Pollock, H. O.: On the Rate of Nitrogen Elimination, J. Biol. Chem. **46**:475 (May) 1921.

6. Marshall, E. K., and Davis, D. M.: J. Biol. Chem. **18**:53, 1914.

7. Palmer, W. W., and Van Slyke, D. D.: Studies of Acidosis, J. Biol. Chem. **32**:500, 1917.

8. Reismann, S. P., and Reimann, H. A.: Blood Bicarbonate Levels Following Administration of Sodium Bicarbonate, J. Biol. Chem. **46**:493 (May) 1921.

occurred. At no time during the above period did the concentration of the blood nitrogen reach the expected level. Since only 4.96 gm. urea were excreted, one cannot readily assume that the failure of the rise in the blood urea is due to rapid elimination. There are still 10.04 gm. to be accounted for. An analysis Table 1, which shows the urea nitrogen concentration in the blood one hour after giving the urea in each case, shows a marked irregularity in the increase. Since all the cases recorded are those with nephritis of varying degrees, a much greater increase should occur in those cases of the more advanced type. Such an increase is markedly conspicuous by its absence. For example, Case 50, which is clinically a case of kidney disease, markedly advanced, with retinal changes, and in a pre-uremic state, shows no greater increase after administration of urea than Case 5 whose only evidence of nephritis is the presence of albumin and casts in the urine. Lack of absorption of the urea in this advanced case certainly seems to have occurred.

Certain other factors apparently come into play in the excretion of urea. Ambard and Weil have shown, and this has been further exemplified by McLean,[9] that at least in the normal case a relation exists between the concentration of urea in the blood and its rate of excretion. Further studies by Austin, Stillman, and Van Slyke[10] although with somewhat different results show again that some relation exists.

Disregarding all these previous considerations it does not even then seem possible that this test unlike all others has a general application. The little knowledge that we have regarding kidney function has shown that disturbances which occur in nephritis show many variations. One type may show faulty excretion of water, another of salt, another of nitrogen, and another of the various dyes. Some show a combined picture of all these disturbances. Animal experimentation has repeatedly shown this. Folin and Denis[11] have had the rare opportunity of studying the kidney function in the human being following an operation of a double ureterostomy. They showed that excretion of urine by the kidney can be subdivided into a number of more or less independent excretions. In moderate hydronephrosis complicated by pyelitis the damage is not uniform. Phosphorus excretion does not correspond to chloride excretion. Creatinin and uric

9. McLean, F. C.: The Numerical Laws Governing the Rate of Excretion of Urea in Man, J. Exper. M. **22**:212, 1915.

10. Austin, J. H.; Stillman, E., and Van Slyke, D. D.: Factors Governing the Excretion Rate of Urea, J. Biol. Chem. **46**:91, 1921.

11. Folin, O., and Denis, W.: Some Observations on the Selective Activity of the Human Kidney, J. Biol. Chem. **22**:321, 1915.

acid do not vary together. Recently Oliver [12] has shown that urea is found in a greater concentration in the proximal convoluted tubules, much higher than that of the blood, or of any other part of the tubules. Therefore, damage to this part of the kidney would naturally alter the excretion of urea more than would damage to any other part of the kidney. Again, many extrarenal factors, especially disturbances of the circulation, would effect the type of urinary excretion.

These observations are borne out by analysis of the cases studied. The following case reports exemplify the possible selective activity of the kidney.

REPORTS OF CASES

CASE 1 (Hosp. No. 2014-21).—Female, aged 40, admitted to the Montreal General Hospital with a clinical diagnosis of acute nephritis and general anasarca.

Urinalysis.—Albumin, 4 plus; blood and epithelial casts, red blood cells.

The patient was placed on the routine orders of restricted fluids, salt free diet, purgation, hot packs, and improvement was noted daily.

TABLE 4.—CLINICAL COURSE OF CASE 1

Date	Urine					Blood		Urea Concentration per Cent.		Phenolsulphonephthalein per Cent. in 2 Hours
				Night Urine						
	C.c.	Albumin Gm. per Liter	NaCl Gm. per Day	C.c.	Per. Cent. N Conc.	Urea N, Gm. per 100 C.c.	Creatinin, Gm. per 100 C.c.	1st Hour	2d Hour	
May 13	1,160	3.0	3.4	...	.....	16	2.1	1.73	1.68	42
May 14	1,160	2.3	4.0	500	0.540					
May 15	680	2.1	7.0	400	0.708	16	2.0	1.20	1.23	50
May 16	950	2.0	5.7	400	0.920	21	1.4	1.20	1.56	56
May 17	975	2.0	4.0	375	0.588					
May 18	500	1.7	2.5	250	0.763	16	1.2	1.20	1.32	62
May 19	980	0.3	...	450	0.728					

There was an average of three diarrheal stools per day.

In this case it will be noted that although the "urea concentration test" showed impairment in function, the nocturnal urine test gave the same information. Neither the "urea" nor the nocturnal urine test showed any quantitative change indicating the progress towards recovery. Recovery was shown by the elimination of fluids greater than intake, a constant excretion of salt with no intake of salt, an increase in the two-hour excretion of phenolsulphonephthalein, a gradual loss of edema, and a general improvement clinically. The patient on discharge from the hospital still showed a low concentration of urea in the "urea concentration test," and also a low nitrogen concentration in the nocturnal urine test.

12. Oliver, J.: Mechanism of Urea Excretion, J. Exper. M. **32**:177 (Feb.) 1921.

CASE 2 (Hosp. No. 1896-21).—Male, aged 42, admitted to the Montreal General Hospital with a clinical diagnosis of acute nephritis.

The patient was too ill to carry out complete analyses. From the data obtained, however, it will be noted that there was no apparent disturbance in the nitrogen elimination, neither in the night urine nor in the "urea concentration test." At necropsy the clinical diagnosis of acute nephritis was corroborated.

TABLE 5

Date	Blood		Urine				
			Night Urine		Urea Concentration, per Cent.		Phenol-sulphone-phthalein, per Cent. in 2 Hours
	Urea N, Mg. per 100 C.c.	Creatinin, Mg. per 100 C.c.	C.c.	Per Cent. Nitrogen Concentration	1st Hour	2d Hour	
May 7	18	1.59	...	...	3.1	3.2	43
May 9	..	....	...	...	3.0	3.0	16
May 10	16	1.59	220	2.1	3.2	3.1	10
May 13	..	....	...	...	3.4	3.3	
May 16	21	1.42	150	2.0	3.1	3.0	

This patient died.

CONCLUSIONS

1. There is no one single test for kidney function, which, in our experience, could be used for the purpose of renal diagnosis, to the exclusion of all others.

2. Various types of nephritis show varied responses to each test.

3. The information obtained from the simple nocturnal urine test parallels, in our experience, that obtained from the urea concentration test.

4. Both the "urea concentration test" and nocturnal urine test gave only qualitative information.

5. To properly interpret the results of any test, a correlation with the clinical picture is of paramount importance.

I am very much indebted to the chiefs of the various services in the Montreal General Hospital, without whose cooperation this work could not have been done.

THE ACTION OF THE NITRITES ON THE CORONARY CIRCULATION *

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CHICAGO

The nitrites have been employed in the treatment of angina pectoris since the time of Lauder Brunton, and it is well known that in many instances the pain subsides soon after the administration of a pearl of amyl nitrite or a pellet of nitroglycerin. The beneficial action of the nitrites has been considered by some to be due to the fall of blood pressure, and by others it has been held that these drugs dilate the coronary arteries and thus improve the coronary circulation thereby affording relief from the cardiac distress. Experimental observations designed to determine the soundness of the latter view have led to varying conclusions. Meyer [1] and Schloss [2] observed an increase in the outflow of the coronary vein in the intact heart following the administration of nitrites. Bond,[3] on the other hand, failed to get positive results. Voegtlin and Macht [4] demonstrated a relaxation of coronary arterial rings from the ox and pig that were suspended in oxygenated Locke's solution containing amyl nitrite, sodium nitrite, and erythrol tetranitrite. Loeb [5] concluded that amyl nitrite had very little effect on the coronary vessels of the profused heart.

In the work here reported, observations were made on the action of sodium nitrite and nitroglycerin on the coronary arteries of the dog.

Method.—Healthy young dogs weighing from 12 to 16 kilograms were used in this work. They were anesthetized with ether. An attempt was made to eliminate as far as possible factors which might produce a fall in the arterial pressure, such as profound anesthesia, excessive traumatization of the tissues in the surgical field and hemorrhage. The heart was exposed by sectioning the second, third, fourth and fifth ribs at the left costosternal margin and extending the incision lateralward in the fifth interspace. The free ribs and the sternum were well retracted and a good exposure of the heart was obtained. A slit was made in the anterior wall of the pericardium and extended from the apex upward to the reflection over the great vessels. The heart was

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1. Meyer: Quoted from Sollmann, Manual of Pharmacology, Philadelphia and London, W. B. Saunders Company, 1917.
2. Schloss, Karl: Deutsch. Arch. f. klin. Med. **111**:310, 1913.
3. Bond, G. S.: J. Exper. M. **12**:575, 1910.
4. Voegtlin, C., and Macht, D. I.: J. Pharmacol. & Exper. Therap. **5**:77, 1913.
5. Loeb, O.: Arch. f. Exper. Path. u. Pharmakol. **51**:64, 1903.

slightly suspended by stitching the slit edges of the pericardium to the sternum and the retracted ribs. The left carotid artery was connected with a mercury manometer.

Observations were made on the action of nitroglycerin on the collateral circulation of the distal branches of the left coronary artery. The presence of collateral circulation between the distal branches of the left coronary artery was in a measure determined by noting the extent and degree of cyanosis that appeared distal to the point of ligation of one of these branches. In those instances in which the cyanosis was extensive and of high grade the probabilities of collateral circulation were considered to be slight. In those instances in which the cyanosis was extensive and of high grade the probabilities of collateral circulation were considered to be slight. In those, however, in which the area of cyanosis seemed small we felt justified in assuming that there were probably communicating branches with adjacent vessels. It occurred to us that any dilating action of nitrites on coronary arteries with well established collateral circulation would be manifested by fading of the cyanosis distal to the point of ligation in this vessel. A distal branch of the left coronary artery was thus ligated. As soon as the infarcted area became well demarcated, nitroglycerin $\frac{1}{200}$ grain, was injected into the left ventricular cavity. Careful observations were then made of any change in the color of the infarcted area by two or more independent observers. Nitroglycerin was employed because of the relatively short duration of its action. It was thus considered that any possible change in the cyanotic area would, perhaps, be more apparent.

In other experiments the rate of outflow from the distal branches of the left coronary artery was determined following the administration of sodium nitrite. The artery chosen for the observation was ligated with its accompanying vein at a point as far peripheral as possible. The artery was then carefully dissected free from the cardiac musculature from the point of ligation proximally for a distance of from 1.5 to 2 cm. This was done with as little manipulation and traumatization as possible. The artery was then divided just proximal to the ligation. The wound in the cardiac musculature produced by the dissection was closed by fine silk sutures. The repair of the wound in this manner held the dissected artery up in a position such that the flow from it could readily be caught in a graduate. The flow was collected for thirty seconds prior to and following the administration of 1 gm. sodium nitrite. In each instance three or four determinations were made and the average of these taken. Clots often formed at the sectioned end of the artery and interfered with the obtaining of uniform readings. This difficulty was overcome as far as possible by gently milking the vessel prior to each reading.

In some instances the arterial end was freshened by small sharp scissors. At no time was more than 1 mm. cut away, and it is not believed that this procedure modified the flow to any significant extent.

Observations on Collateral Circulation.—In fifteen dogs observations were made on the effect of nitroglycerin on the collateral circulation of the distal branches of the left coronary artery. In five there was a distinct change in the area of cyanosis distal to the point in which the artery chosen for study was ligated. In four of these the cyanosis practically disappeared within one minute following the administration of the nitroglycerin and coincident with the drop in arterial pressure. The cyanosis returned to its original intensity in from five to seven minutes with the termination of the nitroglycerin action, as indicated by the rise of blood pressure. In each of these five instances the area of cyanosis produced by the ligation was unusually small and the line of demarcation was not very distinct. In six cases questionable results were obtained, and in the remaining four there was no apparent change in the degree of cyanosis following the administration of nitroglycerin. In these ten dogs the cyanotic area seemed relatively large. This was especially true in the latter four.

Observations on Coronary Outflow (Experiment 6)

Reading	Blood Flow in C.c. for Period of 30 Sec.	Blood Pressure	Time	Remarks
First	12.25	120	10:00 a. m.	
Second	12.00	120	10:05 a. m.	
Third	12.40	120	10:08 a. m.	Vessel milked
1 grain sodium nitrite administered				
First	14.50	80	10:13:32	Vessel milked
Second	13.25	80	10:17 a. m.	
Third	14.1	80	10:28 a. m.	End of vessel clipped
Fourth	12.1	115	10:62 a. m.	End of vessel clipped
Fifth	11.6	114	11:05 a. m.	

Observation on Coronary Outflow.—In fourteen other dogs the flow from corresponding distal branches of the left coronary artery was determined before and after the administration of sodium nitrite. In six there was an increase in the rate of flow within two minutes following the injection of the nitrite and this with a drop in the arterial pressure of from thirty to forty points. The accompanying table shows the results of one experiment. In three of these the blood pressure returned to approximately the initial reading in forty-five, fifty and sixty-five minutes respectively. The rate of flow was again determined and the results corresponded fairly well with that made prior to the administration of the nitrite. In the other three, in which there was an increased flow the arterial pressure failed to

return to the initial level after periods of more than an hour. In three the rate of flow remained about the same and in five there was a definite decrease in the output of the coronary vessel following the fall in arterial pressure subsequent to the injection of the sodium nitrite. The negative results in four of the latter were possibly due to faulty technic. In one there was considerably delay in adjusting the mercury manometer. The animal had been under anesthesia for more than an hour before the sodium nitrite was given and the arterial pressure had already begun to fall. In three difficulty was encountered in dissecting the vessel. Here again the period of anesthesia was prolonged. It was also noted that excessive manipulation of the heart in the preparation of the vessel caused marked fluctuations in the blood pressure.

COMMENT

It was noted that there was a wide variation in the extent and degree of the cyanosis that appeared distal to the point of the ligation of corresponding distal branches of the left coronary artery. In some former work [6] in which dogs were allowed to live following the closure of various branches of the left coronary artery there were likewise striking variations in the extent of the cardiac damage found at necropsy. These results indicate that the extent of the collateral circulation between corresponding branches of the left coronary artery varies markedly in the dog. In some instances it would seem that the collateral circulation is well established, while in others very little if any exists. In those in which the area of cyanosis was relatively small the blue color faded following the administration of nitroglycerin. In those, however, in which the area of cyanosis was large there was very little if any change after the injection of nitroglycerin. The former observations seem to indicate that there were communicating branches with the adjacent vessels which were dilated by the nitroglycerin. In the latter instance it was concluded that the collateral circulation was very limited and thus no striking change was anticipated from the nitroglycerin.

In five experiments there was a definite increase in the rate of flow from distal branches of the left coronary artery after the injection of sodium nitrite into the left ventricular cavity, coincident with a drop in the arterial pressure of from 35 to 60 mm. Hg. in the arterial pressure. According to Wiggers [7] the coronary circulation is

6. Smith, F. M.: The Ligation of Coronary Arteries with Electrocardiographic Study, Arch. Int. Med. **22**:8 (July) 1918.

7. Wiggers, C. J.: Circulation in Health and Disease, Lea & Febiger, New York and Philadelphia, 1915, p. 84.

dependent to a marked extent on the arterial pressure. The results in these five instances thus indicate that the coronary arteries were dilated by the sodium nitrite. It is difficult to explain the results in the three instances in which the rate of flow remained the same after the blood pressure had fallen except by assuming that the coronary artery was dilated. The conclusions derived from these results are thus in accordance with those held by Meyer, Schloss and Voegtlin and Macht, namely that the nitrites dilate the coronary arteries.

SUMMARY

The action of nitroglycerin on the collateral circulation between distal branches of the left coronary artery was studied in fifteen dogs. In five instances the area of cyanosis that appeared distal to the point of closure of one of these vessels definitely faded following the administration of nitroglycerin. In six the results were questionable and in four they were apparently negative. The observations in the former five indicated that there was a communication with the adjacent vessels which was dilated by the nitroglycerin. In the latter ten it was concluded that very little collateral circulation existed.

In fourteen dogs the rate of blood flow from distal branches of the left coronary artery was determined before and after the administration of sodium nitrite. In six there was a definite increase in the outflow. In three the rate remained about the same and in four it was decreased.

A SIMPLE AND ACCURATE METABOLISM SPIROMETER

SPIROMETER MEASUREMENT OF OXYGEN CONSUMPTION BY THE REBREATHING METHOD *

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As is commonly known, the essentials of rebreathing types of spirometers comprise a distensible closed space, as an elastic bag or spirometer; a supply of oxygen and means for introducing it into the apparatus; an absorber for removing carbon dioxid; connection for a mouth or nose piece or mask; and means for measuring volume changes in the gas. The subject rebreathes for a definite period, usually ten minutes, and the volume change of gas in the apparatus, after correction for pressure, temperature, and water vapor, indicates the amount of oxygen consumed.

Spirometer.—The spirometer shown in Figure 1 is very satisfactory. It consists of a vital capacity type of spirometer (floating bell form, Fig. 1, A), a soda-lime carbon dioxid absorber (Fig. 1, B), a four way tap (Fig. 1, C), a gas mixing pump (Fig. 1, D), and a tank of oxygen.

The three point suspension of the bell is very desirable. The bell moves vertically with little side sway or rotation and the scale, which is attached to the bell, remains directly behind the reading sight. The sight (Fig. 1, E) is adjustable and may be set instantly against the zero mark of the scale. The scale on one side is numbered from below upward, so that the final reading directly represents the oxygen consumed, no subtraction or other calculation being required. The smallest scale divisions represent 20 c.c.

An important feature is the cap on top of the bell and the extension of the breathing pipe almost to the under surface of the cap when the bell is in the lowest position. The cap and the extension tube prevent accidental entrance of water into the breathing pipe. To further guard against water from entering the absorber, the outer end of the breathing pipe is directed upward for some inches. A small brass tap is attached to the lowest point of the pipe and serves the triple purpose of providing a drain, of introducing oxygen, or of withdrawing samples of gas for analysis.

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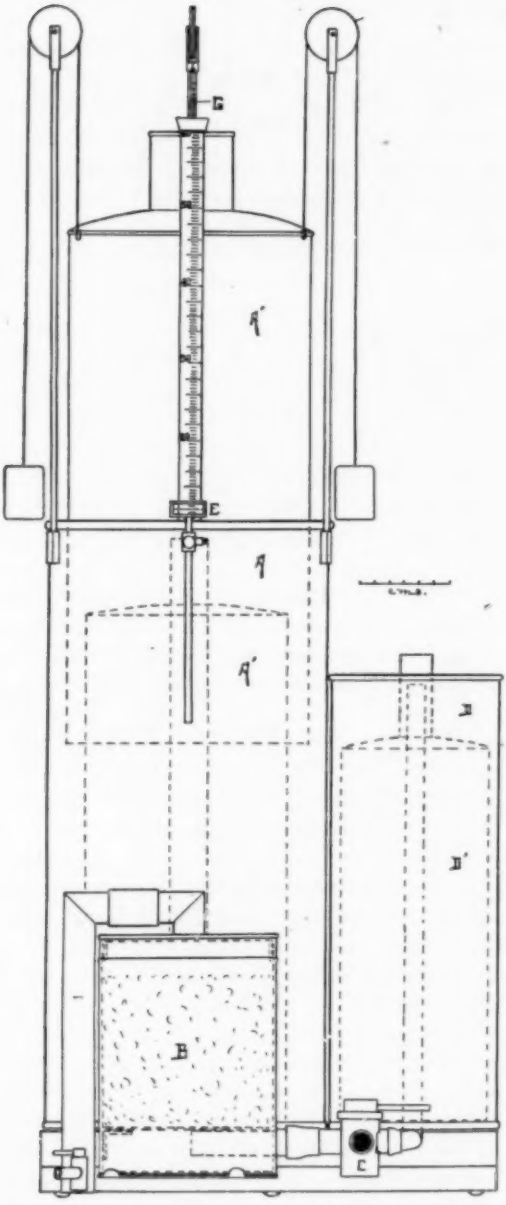

Fig. 1.—Closed circuit spirometer for measuring oxygen consumption. A, jacket; A′ and A′, bell and inside can of spirometer jacket, respectively; B, carbon dioxid absorber; C, four-way tap; D, mixing pump; D′, bell of pump; E, adjustable sight; G, thermometer.

The design of the sight for reading the scale, viz. a fine cross wire set in a flattened tube, permits rapid and very accurate readings.

Absorber.—The form of absorber shown in Figure 1, B gives very satisfactory results. It consists of a copper can provided with a removable top. A tube is attached in the center of the top and another passes horizontally through the side of the can near the bottom to a point

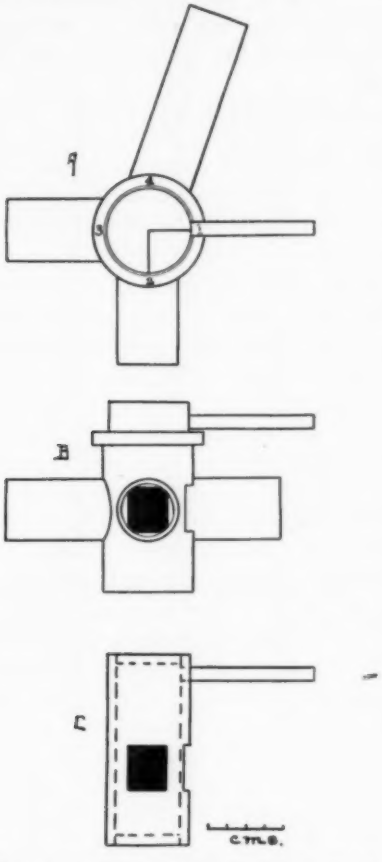

Fig. 2.—Four way tap. A, tap; B, front; C, plug.

about half an inch above the center of the bottom. These tubes are for connecting the absorber with the spirometer and with the subject. A false bottom consisting of a close fitting brass wire cloth disc is supported about an inch from the bottom so that the lower tube opens into an air space and is protected from contact with the soda-lime, with

which the can is filled from the false bottom to within an inch of the top. Thus air pressures above and below the ends of the cylindrical mass of absorbing material are uniform. The lid is sealed by means of a strip of adhesive tape or by painting with melted paraffin. The top is connected to the spirometer pipe by a short coupling of tight fitting rubber tubing. The lower tube is connected with the four way tap.

Tap.—The tap (Fig. 2) serves to connect the spirometer through the absorber with the pump, the subject, or the outside air. The rotating portion of the tap is hollow and provided with two openings spaced 90 degrees apart.

In the first position of the tap, the absorber is shut off and the subject breathes room air. Position two is a quarter turn (clockwise, i. e. to the right) and switches the subject to the absorber and thus to the air in the spirometer, at the same time closing the opening to the outside. Position three connects the absorber with the pump, and position four connects the pump with the outside air.

Pump.—The pump essentially is a miniature spirometer of the form described, minus counterpoise weights, etc. (Fig. 1, D). It is mounted alongside the spirometer and connected with the absorber by means of the four way tap. At the end of the observation the bell of the pump is lifted and lowered by hand until the gas volume becomes stabilized. Before the initial or zero reading and again before the final reading the tap is turned to position three, which connects the spirometer and pump and the air is passed back and forth through the absorber. This soon equalizes and stabilizes temperature and water vapor conditions and ensures removal of all carbon dioxid.

Method of Using.—The tap is turned to position four to ensure that the pressure in the pump connections is atmospheric. It is then turned (clockwise) to position two (spirometer with air through subject connector) and the spirometer bell set to read say 1,000 c.c., the sight having been set as low as it will go. The tap is turned (clockwise) to position three. The tube from the oxygen tank is connected to the filling tap and the tap opened slowly to let in oxygen until zero on the scale is about 100 c.c. above the sight. The oxygen tank and the filling taps are closed. The sight is set on the zero mark and the pump bell raised and lowered five times. The scale is read. The air is pumped again and the scale read and this is continued until the readings check. The tap is turned (clockwise) to position four and then to position one The sight is set on zero, the temperature noted and the subject connected. When breathing is regular, at the end of an expiration the tap is turned (clockwise) to position two and the time noted. A wisp of cotton held near the opening in the tap serves as an index of the respiratory stages. To terminate the test, the spirometer bell is

observed and during a period of regular breathing, at the instant the bell reaches the top of an excursion (end of expiration) the tap is turned (clockwise) to position three, the time noted and the subject disconnected. The scale is read and the air pumped and read and this is continued until the readings check. The temperature is noted.

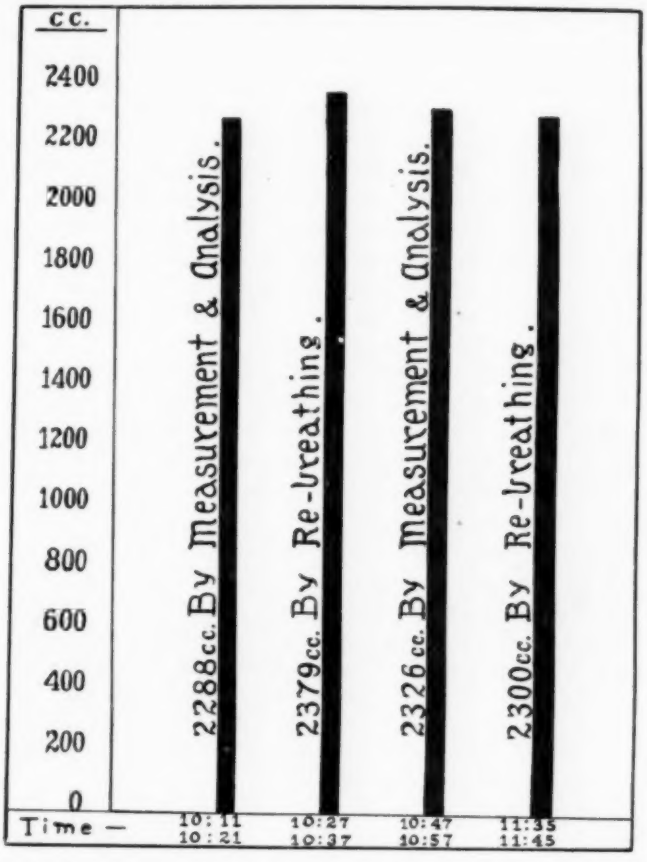

Fig. 3.—Oxygen consumption as measured alternately by a Tissot form and the closed circuit form of spirometer. Water valves were used with the Tissot form.

The design of the sight is well adapted to catch readings near the beginning and near the end of the test if desired. Such readings are desirable as checks, and in no way interfere with the stationary readings described.

For a new test, the sight is set at the lowest point. The tap is turned to position two. The mouthpiece to the subject being disconnected, by raising and lowering the spirometer bell by hand, the air remaining from the previous test is expelled and the spirometer refilled with fresh air and oxygen as described above.

COMMENT

Under stabilized conditions, as uniform room temperature and absence of drafts, and with good soda lime, changes in the initial total volume readings induced by circulating air through the absorber range from zero to 20 c.c., while the changes induced in the final reading usually range from about 20 to 40 c.c. Under such conditions results accurate to within less than two per cent. can be obtained with an ordinary vital capacity type of spirometer, a soda lime absorber and a two way tap. An ordinary hot water bag can be connected on the tube to the subject and used in place of the pump. By raising and lowering the spirometer bell by hand the air is circulated through the absorber and thus error can be largely eliminated.

Different samples of soda-lime purchased in the open market show great variations in carbon dioxid absorbing powers, some samples being several times more efficient than others. The most satisfactory method is analysis of the gas from the spirometer at the end of the test. With a satisfactory sample of soda-lime not more than a trace of carbon dioxid should be present.

The results from a series of alternate observations made by measuring and analysing the expired air by means of a large bell spirometer and gas analyser and the results obtained with the rebreathing method show the range of the normal variations in successive tests as well as the similarity of the results by the two methods (Fig. 3). Sometimes successive observations by either method may give results varying not more than 10 c.c. for a ten minute period but uniformity within such narrow limits is not to be expected physiologically. Nor is it reasonable to assume corresponding uniformity of air volume in the lungs at the beginning and end of the test.

It may be of interest to note, in conclusion, that the sheet metal work on the spirometer, absorber and pump was done by an ordinary tinsmith and the total cost at regular rates for material (copper) and labor was $21. The other parts were made in our shop.

SUMMARY

A convenient and accurate form of closed circuit spirometer is described.

THE EFFECT OF THE INGESTION OF FOODSTUFFS ON THE RESPIRATORY EXCHANGE IN PULMONARY TUBERCULOSIS *

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With the technical assistance of G. F. Soderstrom
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Elaborate studies of the effect of foodstuffs on the respiratory metabolism have been made by Rubner [1] and Lusk,[2] who are the principal workers in this field. Reference should be made to the latter for an excellent review of the subject. These investigations were concerned chiefly with the calorimetric observations, in which the magnitude of pulmonary ventilation was not measured.

In a previous communication [3] the effect of protein ingestion on the heat production of two tuberculous patients and two normal subjects was found to be identical. On a priori grounds the assumption was made that the pulmonary ventilation varies directly with the metabolism. Confirmatory evidence on this point is given by Peabody [4] who shows the parallelism between the minute volume of air expired and the level of metabolism in patients with exophthalmic goiter. The general validity of the assumption is well demonstrated by Pearce,[5] who showed that total ventilation and cardiac volume output, within the capacity of the organism, vary directly with the rate of oxygen consumption.

Since the problem of selecting a proper diet for patients with pulmonary tuberculosis involves a knowledge of the effect of food ingestion on the function of the diseased lungs, it seems important to present the data of a few experiments bearing on this point.

Technic.—The apparatus used for this work was a Tissot spirometer. This spirometer has a capacity of eighty-four liters. The bell is counterpoised by a container into which water siphons, so that as the buoyancy of the bell diminishes the weight of the counterpoise increases by an equivalent amount. A description of this device is to be found in the monograph by Carpenter.[6]

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* From the Russell Sage Institute of Pathology in affiliation with the Second Medical Division of Bellevue Hospital.

1. Rubner, M.: Die Gesetze des Energie-verbrauchs bei der Ernährung, 1902.
2. Lusk, G.: Science of Nutrition, Ed. 3, 1917, pp. 223-247.
3. McCann, W. S., and Barr, D. P.: Clinical Calorimetry, Paper No. 29, The Metabolism in Tuberculosis, Arch. Int. Med. **26**:663 (Nov.) 1920.
4. Peabody, F.: Respiration in Disease, Oxford Medicine, **1**:409.
5. Pearce, R. G.: The Cardiorespiratory Mechanism in Health and Disease, Arch. Int. Med. **27**:139 (Jan.) 1921.
6. Carpenter, T. M.: A Comparison of the Methods for the Study of the Respiratory Exchange, Carnegie Inst. of Washington, D. C., Pub. No. 216.

The wire connecting the spirometer bell and the counterpoise runs over a pulley 12 inches in diameter. On this pulley are graduation marks for each liter. Readings are made to the first place of decimals. These calibrations were made with a Bohr meter at 23 C. Since calculations were to be based on dry gas volume, it was necessary to apply calibration corrections. These corrections were made as follows: A metal bomb containing dry oxygen was weighed. The gas was then allowed to escape, passing through water into the spirometer. At intervals of five liters on the spirometer scale the bomb was closed and again weighed. The difference in weight equals the weight of oxygen admitted to the spirometer. The temperature of the spirometer and the barometer reading were noted. The observed reading of the gas volume in the spirometer was then corrected for aqueous vapor tension at the observed temperature, to 0 C. and 760 mm. dry. This dry gas volume was then compared with the volume which the known weight of dry oxygen gas would occupy at 0 C. and 760 mm. dry. This is obtained by multiplying the weight of oxygen by 22.4/32. In this way a calibration curve was constructed. The oxygen used contained about 0.4 per cent. chiefly argon.

The valve used to separate inspired and expired air was made by G. F. Soderstrom. A sketch of this valve is shown in the accompanying figure. After having devised the valve it was found that a similar valve had been described by Tigerstedt.[7] The mouthpiece used was identical with that of the American gas masks.[8] The nose was then closed with a spring clip.

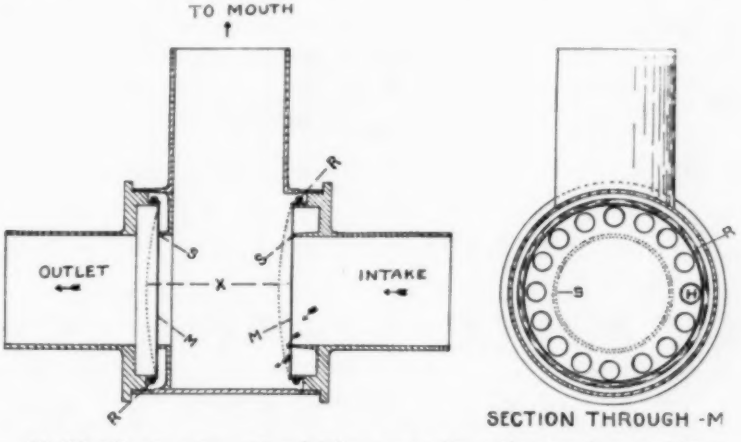
Patients were prepared in the usual manner for basal metabolism determinations. No food was allowed after 4:30 or 5 p. m. on the preceding day so that the basal determinations were generally made at least sixteen hours after eating. A period of absolute rest of twenty minutes or more before the test was observed in all bed patients and thirty minutes at least of absolute rest reclining in a steamer chair for all normal subjects or ambulatory patients.

Many persons on the first occasion of breathing through the mouth, with the nose closed by a clip, will alter their breathing from the normal type. The invariable tendency is to over ventilate either by increasing the depth of breathing, or by increasing the rate. Some patients can never be trained not to do this. In the experiments given here subjects were allowed to become accustomed to the apparatus before the beginning of the experiment. The rate of respiration was counted before

7. Tigerstedt, R.: Lehrbuch der Physiologie des Menschen, Leipzig, **1**:89, 1902. The valve is ascribed to Lovén, but the original reference is not given.

8. This was obtained from the Siola Rubber Manufacturing Co., 103 Park Ave., New York.

inserting the mouthpiece and the normal type of breathing was closely observed. After adjusting the mouthpiece and nose clip the respirations were again observed until they again became of normal rate and type. At this time 8 or 10 liters of expired air were admitted into the spirometer in order to get the approximate minute volume and to fill the dead space of the apparatus with air of the same composition as that to be measured and analyzed. This gas was expelled as completely as possible, i.e. to zero mark. If the subject continued to breathe normally, the three-way valve opening into the spirometer was thrown open at the end of an expiration and the time noted. After from six to ten minutes, depending on the minute volume expired, the valve was closed at the end of expiration and the time noted.



Modified Lovén valve. M and M′ are very thin rubber membrane, which in the closed position is in contact with the rims S of the valve seats. The membranes are held in place by the rings R, which slip on and off. The holes in the membrane H, are burned through the rubber after it is fastened in place. Contact of M with S is made more secure by moistening the membrane with glycerin. X shows the open position of membranes, which open and close reciprocally.

Movement on the part of the patient, distress from tickling sensations in throat or a desire to cough were made matters of note. The manner of closure of the lips over the mouthpiece was carefully watched. If there was any doubt as to the possibility of leaks about the lips or nostrils a lather of shaving soap was applied. A leak would be detected by the formation of a bubble.

It will be seen, therefore, that the valve which was used required considerable care. For this study it was preferred to the other forms in use because of its small dead space, the ease with which it opened

TABLE 1.—Data on Five Normal Subjects and Five Tuberculosis Patients

Name, Age, Sex, Surf. Area, Ht.-Wt. Formula	Date	Volume Expired, Liters S.T.P.D. per Hr.	Gas Analysis CO_2 %	Gas Analysis O_2 %	Calories per Hr.	R. Q.	Metabolism Variation from Av. N. ± %	Temp., Degree F.	Pulse Rate per Min.	Resp. Rate per Min.	Urine N per Hr., Gm	Remarks	Diagnosis
John S. ..... 21 yrs. ♂ 1.69 Sq. M.	9/ 3/20	274.6	{4.08 {4.05	{16.51} {16.56}	60.4	0.898	− 9	.....	68	16	.....	Basal. Ingested 350 gm. lean beef + 10 gm. butter	Normal control
	9/ 3/20	384.8	3.59	16.51	84.6	0.766	+27.5	.....	62	16	.....	127 min. after meal	
	9/10/20	332.7	{4.17 {4.12	{16.16} {16.17}	79.0	0.836	+19	.....	...	..	.....	116 min. after meal	
	9/10/20	292.1	4.17	15.86	73.6	0.780	+11	.....	64	12	.....	296 min. after meal	
Abr. M. ..... 21 yrs. ♂ 1.42 Sq. M	11/29/20	578.5	{2.20 {2.17	{18.40} {18.42}	72.7	0.824	+30	101.6	108	36	.....	Basal.....	Acute pneumonic phthisis; extensive bilateral involvement
	11/30/20	554.4	{2.11} {2.14}	.....	....	.....	....	101.4	108	36	.....	Basal. Ingested 140 gm. fat in cream	
	11/30/20	613.0	{2.24 {2.25	{18.30} {18.29}	80.3	0.807	+43	100.6	120	34	.....	100 min. after meal	
	12/ 3/20	602.8	{2.07} {2.09}	18.44	82.1	0.782	+47	100.4	135	44	.....	139 min. after	
	12/ 3/20	656.2	{1.92} {1.96}	18.42	81.8	0.715	+46	102.8	129	40	.....	296 min. after	
Fred R. ..... 41 yrs. ♂ 1.92 Sq. M.	12/ 2/20	540.5	{2.14 {2.17	{18.50} {18.50}	65.5	0.848	+12	98.0	90	30	.....	Basal.....	Pulmonary tuberculosis; very extensive bilateral infiltration with numerous cavities throughout
	12/11/20	552.2	{2.27 {2.21	{18.20} {18.21}	75.0	0.770	+28	100.0	102	30	.....	Basal. Ingested 290 gm. lean beef + 6 gm. butter	
	12/11/20	608.7	{2.51} {2.51}	.....	....	.....	....	100.8	114	30	.....	76 min. after meal	
	12/11/20	664.4	2.40	18.17	91.0	0.840	+37	100.8	114	34	.....	206 min. after	
C. H. L. ..... 26 yrs. ♀ 1.56 Sq. M.	12/30/20	266.2	{4.18 {4.21	{16.46} {16.41}	59.7	0.913	+ 3	.....	66	12	0.483	Basal. Slight overventilation; ingested 150 gm. lean beef	Normal
	12/30/20	277.6	{4.08 {4.08	{16.57} {16.53}	60.8	0.906	+ 5	.....	68	12	0.052	103 min. after meal	
	12/30/20	269.0	4.09	16.46	60.1	0.886	....	.....	...	..	0.567	256 min. after	
	12/30/20	245.6	4.26	15.89	61.6	0.904	+ 7	.....	...	..	0.465	335 min. after	

W. ..... 26 yrs. ♂ 1.91 Sq. M.	12/31/20	304.2	{4.26 {4.27	{15.97 {15.99	75.0	0.825	0	.....	60	12	2.146	Basal. Ingested 460 gm. lean beef	Normal
	12/31/20	341.2	4.23	16.17	81.0	0.855	+ 7	.....	60	12	0.247	80 min. after meal	
	12/31/20	337.1	4.25	15.93	84.0	0.810	+11	.....	60	12	0.247	149 min. after	
	12/31/20	349.6	4.03	16.13	83.5	0.798	+11	.....	60	12	0.247	210 min. after	
J. O'C. ..... 49 yrs. ♂ 1.59 Sq. M.	12/14/20	434.0	{2.42 {2.42	{18.04 {18.07	62.0	0.806	+ 3	100.8	72	24	.....	Basal.....	Tuberculosis, pulmonary; moderately advanced infiltration of both upper lobes
	12/23/20	402.0	{2.49 {2.49	{18.42 {18.40	61.0	0.969	0	100.6	72	27	.....	Basal. Constant desire to cough; Ingested 100 gm. lean beef + 3 gm. butter	
	12/23/20	389.0	{2.82 {2.82	{17.96 {17.93	58.0	0.921	— 4	100.8	75	24	.....	74 min. after; desires to cough	
	12/23/20	411.0	{2.46 {2.44	{18.23 {18.22	55.3	0.874	— 8	101.4	72	24	.....	152 min. after; breathing normally	
Geo R. ..... 35 yrs. ♂ 1.02 Sq. M.	1/26/21	434.2	{2.73 {2.74	{17.76 {17.72	67.6	0.816	+ 6	98.8	75	16	.....	Basal. Ingested 350 gm. lean beef	Pulmonary tuberculosis; advanced bilateral infiltration with large cavities; fistula in ano
	2/ 8/21	523.0	{2.87 {2.83	{17.64 {17.63	8.69	0.822	+33	99.4	88	20	.....	77 min. after meal	
	2/ 8/21	544.2	{2.73 {2.73	{17.73 {17.71	87.0	0.803	+34	99.6	80	25	.....	188 min. after	
J. V. B. ..... 43 yrs. ♂ 1.51 Sq. M.	5/18/21	487.7	{2.56 {2.58	{17.85 {17.85	74.9	0.789	+29	99.8	80	19	.....	Fasting, not basal. Slight movement; body tense; ingested 102 gm. glucose in "Kaffee Hag"	Pulmonary tuberculosis; dense infiltration of right upper and middle lobes with multiple excavations; large cavity left upper lobe, below which consolidation with small cavities
	5/18/21	573.4	{2.56 {2.53	{18.37 {18.36	73.9	0.969	....	100.4	108	21	.....	1 hours after meal	
	5/18/21	553.5	2.63	18.25	74.3	0.963	....	100.4	108	18	.....	90 min. after	
G. M. ..... 32 yrs. ♀ 1.57 Sq. M.	5/29/21	203 8	{3.91 {3.93	{15.82 {15.86	51.3	0.723	—11	97.8	70	7	.....	Basal. Ingested 100 gm. glucose in "Kaffee Hag"	Control
	5/29/21	242.0	3.81	16.15	57.5	0.750	0	.....	76	12	.....	37 min. after; changed type of breathing	
	5/29/21	269.4	{3.88 {3.84	{16.60 {16.64	57.7	0.863	0	.....	76	9	.....	87 min. after; quiet normal resp.	
Wm. U. ..... 42 yrs. ♂ 1.65 Sq. M.	1/19/21	227.6	{3.22 {3.22	{16.81 {16.85	46.5	0.735	—27	94.0	42	9	0.346	Basal. End of 16 days' fasting, wt. 51.7 kg., 1.65 sq. m.; ingested 105 gm. protein	Normal man physically; control; voluntary subject of fasting experiment
	1/19/21	273.6	{3.73 {3.70	{16.28 {16.32	62.9	0.754	— 1	.....	...	9	0.142	53 min. after meal	
	1/19/21	304.6	{3.56 {3.52	{16.57 {16.60	65.7	0.769	+3.5	.....	64	8	0.580	110 min. after	
	1/19/21	301.4	{3.51 {3.52	{16.42 {16.48	67.0	0.734	+5.4	98.0	66	9	0.490	209 min. after	

(pressure of from 1 to 2 mm. water) and the complete lack of leakage back. The absence of these virtues might have made considerable difference in the volume of air respired.

Samples of air from the spirometer were drawn into special sampling bottles [9] over a solution consisting of equal parts of glycerin and saturated sodium chlorid solution. The sample of air can be kept unchanged for at least twenty-four hours over this solution.[10] In our hands this has been fully as satisfactory as mercury and much cheaper.

The air analyses were made with a modification of Henderson's [11] air analyser. In its original form the apparatus had a very short water jacket. In our apparatus a long water jacket was used and in place of the original absorber shell for carbon dioxid absorption a bulb was used very much as in the Haldane apparatus. These are minor details. The essential feature of the apparatus is the very ingenious four-way stopcock of Henderson.

Gas burets were recalibrated with mercury and calibrations and technic were checked by analyses of pure outside air. The values obtained for carbon dioxid vary from 0.02 to 0.03 per cent. and for oxygen from 20.93 to 20.97 per cent. In calculation Haldane's value for oxygen in outside air was used: 20.93 per cent. In analyses of expired air duplicate oxygen analyses were checked within 0.04 per cent. except in one or two cases. The greatest variation allowable between duplicates is 0.06 per cent.

A description of the calculation is given very clearly by Boothby and Sandiford.[12] We have used a slightly different set of tables for correction of gas volumes. They may be found in convenient form by Wells.[13]

DISCUSSION OF RESULTS

Experimental data are given in Table 1. Ten subjects were used, five of whom were normal. The most striking thing on first inspection of this table is the difference between tuberculous and normal individuals in volume expired per unit of time. The explanation of this is quite obviously to be found in the reduced vital capacity of the tuberculous patients. Peabody [14] has shown that normal individuals may increase

9. Devised by Dr. Donald Van Slyke of the Rockefeller Institute for Medical Research.

10. We are indebted to Dr. Wm. C. Stadie for this point in technic.

11. Henderson, Y.: The Haldane Gas Analyser, J. Biol. Chem. **33**:31, 1918.

12. Boothby, W. M., and Sandiford, I.: Basal Metabolic Rate Determinations, 1920, W. B. Saunders Company, Philadelphia.

13. Wells, H. L.: Tables for Chemical Calculations, 1903, Henry Holt, New York, p. 10.

14. Peabody, F.: Cardiac Dyspnea, A. J. M. Sc. **155**:100, 1918.

the tidal air up to one third of the vital capacity, beyond which point further increase in respiratory exchange must be accomplished by increasing the rate of respiration. Since the dead space has a relatively constant volume, increasing the rate of respiration decreases the ratio of effective minute volume to total minute volume expired. This results in a lower percentage of carbon dioxid and a higher percentage of oxygen in expired air, other factors being equal.

Referring to Table 2 it will be seen that for each of the five normals and five patients the minute volume and tidal air have been tabulated from the data for each basal period. For the normals the average minute volume was 4.25 liters, average respirations were 11 per minute and average tidal air 397 c. c. This is 11 per cent. of the average normal vital capacity as estimated from the surface area by the formula of

TABLE 2.—MINUTE VOLUME AND TIDAL AIR

Name	Volume Expired, Basal Liters per Hr.	Resp. per Min.	Minute Volume, C.c Expired	Tidal Air, C.c.	Effective Minute Volume, C.c. *	CO_2 C.c. per Min. Produced	Ratio of Total Min. Vol. to CO_2 per Min.	Ratio of Effective Min. Vol. to CO_2 per Min.
Normal:								
John S.	274.6	16	4,577	286	2,497	185	24.7	13.5
C. H. L.	266.5	12	4,437	370	2,877	185	23.9	15.5
W.	304.2	12	5,070	423	3,510	214	23.7	16.4
G. M.	203.8	7	3,397	485	2,487	122	25.7	18.9
Wm. U.	227.6	9	3,793	421	2,623	121	31.3	21.6
Average	.....	11	4,255	397	2,799	167	25.9	17.2
Tuberculous:								
Ab. M.	578.5	36	9,641	268	4,961	208	46.3	23.8
Fred R.	540.5	30	9,008	300	5,108	192	46.9	26.6
J. O'C.	434.0	24	7,233	301	4,113	173	41.8	23.8
Geo. R.	434.2	16	7,237	452	5,158	198	37.5	26.7
J. V. B.	487.7	19	8,128	428	5,668	206	39.5	27.5
Average	.....	25	8,249	350	4,799	195	42.5	25.7

* Effective minute volume = total minute volume minus respirations per minute × 130 c.c. The average dead space assumed to be 130 c.c.

West.[15] In the tuberculous series the average minute volume was 8.25 liters, average respiration rate 25 per minute and average tidal air 350 c. c. The value for the tidal air must be approximately maximal inasmuch as in all of the tuberculous cases increases in metabolism were accompanied by accelerated respirations. If the same ratio of maximal tidal air to vital capacity obtains in tuberculosis as in normals this would indicate an average vital capacity of from 1,000 to 1,100 c. c. This figure is undoubtedly lower than these subjects would have shown if the vital capacity were determined in the erect posture. It probably represents the reduced vital capacity of the recumbent posture.

15. West, H. F.: A Comparison of Various Normal Standards for the Normal Vital Capacity of the Lungs, Arch. Int. Med. **25**:306 (March) 1920.

In Table 2 the effective minute volume, or alveolar ventilation for each individual has been calculated on the assumption that the dead space was 130 c. c. This gives an average effective alveolar ventilation for the five normals of 2,799 c. c., and for the five patients of 4,799 c.c. However, it will be seen that the average amount of carbon dioxid eliminated per minute was higher in the tuberculous series, 195 c.c. per minute for the patients against 167 c.c. per minute for the normals. The ratio of total ventilation to volume carbon dioxid eliminated is almost twice as large for the tuberculous cases as for the normals. Even when they are compared on the basis of the ratio of effective alveolar ventilation to carbon dioxid elimination the ratio is again less for the normals: 17.2 for normals and 25.7 for patients. This is in keeping with the results of experiments on the effect of artificially elevating body temperature. Hill and Flack [16] called attention to the overventilation which occurs in subjects immersed in hot boths. A marked fall in alveolar carbon dioxid tension was noted. Haggard [17] has shown that under these circumstance there is a diminution of the ratio (H_2CO_3:$NaHCO_3$), which he believed to be due to the decreased solubility of carbon dioxid at elevated body temperatures. He found that the alveolar carbon dioxid tension was reduced, and that the carbon dioxid combining power of the blood was not correspondingly changed.

It should be pointed out, however, that, in the basal observations which are tabulated in Table 2, the elevation of temperature was in no case very high, so that there may be other unknown factors which enter into the production of the overventilation of these patients.

In Table 3 are tabulated the comparisons of the percentage increases in heat production and total pulmonary ventilation after the ingestion of varying amounts of foodstuffs. It will be seen at once that the parallelism is very close in both normal and tuberculous subjects.

In considering the effect of protein ingestion it will be seen that there is considerable variation in the amount of increase of heat production. There are several factors which determine the extent to which protein will increase heat production: First, the amount of protein relative to the size of the individual subject; second, the previous nutritive condition of the subject or the level of endogenous protein metabolism at the time of ingestion of protein food. Environmental temperature plays a part. The development of our knowledge of these

16. Hill, L., and Flack, M.: The Influence of Hot Baths on Pulse Frequency, Blood Pressure, Body Temperature, Breathing Volume and Alveolar Tension of Man, J. Physiol. **38**:57, Proc., 1909.

17. Haggard, H. W.: The Alteration of the Carbon Dioxid Ratio (H_2CO_3: $NaHCO_3$) in the Blood During Elevation of Body Temperature J. Biol. Chem. **44**:131, 1920.

factors is the result of the researches of Rubner [1] and Lusk.[2] The amounts of protein ingested have been expressed in terms of grams per square meter of body surface area. In the cases of C. H. L. and J. O'C. the amount of protein ingested was not sufficient to increase the heat production; it served merely to replace endogenous protein.

External temperature probably plays no part in these experiments since all subjects had sufficient covering to maintain perfect comfort. This gives an evironmental temperature of about 33 C. at the skin surface. The effect of previous nutritive condition is very strikingly shown in the case of William U., who ingested protein after sixteen days of complete starvation. Subject John S. habitually lives on a very low protein diet. Subject W. lives on a high protein diet. His nitrogen excretion per hour before ingesting protein was higher than that observed subsequently. Tuberculous subjects Fred R. and Geo. R. behaved similarly to the four subjects studied by McCann and Barr [3] in the respiration calorimeter.

TABLE 3.—Percentage Increase in Heat Production and Pulmonary Ventilation After Eating

Name	Amount Foodstuff Ingested, Gm.	Calories per Hr. Basal	Maximum Calories per Hr. after Food Ingestion	Increase Heat Produced, per Cent.	Increase Ventilation, per Cent.	Time of Maximum Increase Hrs. after Ingestion	Grams Protein per Sq. Meter Body Surface
John S.	73 protein	60.4	84.6	40	40	2	43
W.	96 protein	75.0	84.0	12	11	2½	50
Wm. U.	105 protein	46.5	67.0	44	32	3½	64
C. H. L.	31 protein	59.7	61.6	3	..	5½	20
Fred R.	61 protein	75.0	91.6	22	20	3½	40
J. O'C.	21 protein	62.0	55.3	(—11)	(—5)	2½	13
Geo. R.	73 protein	67.6	87.0	29	25	3	45
Ab. M.	140 fat	72.7	82.1	12	14.5	2½	
G. M.	100 glucose	58.1	57.7	12	22	1½	
J. V. B.	100 glucose	74.9	74.3	0	17	1-1½	

That protein has a specific dynamic action in tuberculosis brings this disease into sharp contrast with typhoid fever. In the latter disease the endogenous protein metabolism is already high at the time of ingesting protein, which merely replaces endogeous protein.[18] McCann and Barr [3] have shown that the level of protein metabolism in tuberculosis is not high, so that ingestion of protein increases the total oxidative processes.

Lusk,[2] quoting Rubner, states that when 100 per cent. of the basal requirement of energy is ingested as meat there is an average increase

18. Coleman, W., and DuBois, E. F.: Calorimetric Observations on the Metabolism of Typhoid Patients With and Without Food, Arch. Int. Med. **15**:2 (Jan.) 887 (June) 1915.

of 36.7 per cent. in the twenty-four hour heat production, if ingested as fat, the metabolism is raised 12.7 per cent. and if as sugar, 5.8 per cent.

Murlin and Lusk [19] and Magnus Levy [20] find somewhat lower figures for the specific dynamic action of fat than those of Rubner. For each 100 calories of ingested fat the metabolism is increased: Rubner, 12.7 calories; Murlin and Lusk, 4.1 calories; and Magnus Levy, 2.5 calories.

In the case of Abr. M., ingestion of 1,312 calories as fat increased the heat production 12 per cent. in from two to five hours. The ingestion of only 410 calories as glucose in the case of J. V. B. caused no increase in metabolism but increased the ventilation 17 per cent., and in the case of G. M. the metabolism rose 12 per cent. and the ventilation rate 32 per cent. Thus, it is seen that the greatest number of calories may be ingested in the form of fat with the least effect on the total ventilation. A marked increase in ventilation occurs during carbohydrate oxidation in spite of a small specific dynamic action. This is due to the relatively greater quantities of carbon dioxid to be eliminated, or, in other words, to the higher respiratory quotient of carbohydrate metabolism. Confirmatory evidence on this point has been found in the work of Benedict and Carpenter.[21] These authors studied the effect of the ingestion of many foods on the heat production and gaseous exchange. Unfortunately, in the experiments on fat and protein no data are given regarding the ventilation. However, some of their carbohydrate experiments were made with the Tissot spirometer. They found (p. 231) that the average maximum effects were produced, in the order of greatest to least, by sucrose, levulose, lactose, and dextrose. On page 217, Table 149, subject H. H. A., after ingestion of 100 gm. sucrose the ventilation increased from 4.29 liters per minute to a maximum of 6.86 liters per minute, an increase of 2.57 liters, or 60 per cent. The carbondioxid elimination increased 55 per cent., while the oxygen consumption rose only 14 per cent.

ADDENDA

Description of Experimental Subjects.—It should be emphasized that all of the tuberculous subjects were in an advanced stage of the disease. With the exception of J. V. B., a detailed history will be found for each in a subsequent communication, "The Protein Requirement in Tuberculosis."

19. Murlin, J. R., and Lusk, G.: J. Biol. Chem. **22**:15, 1915.
20. Magnus, L. A.: Arch. f. d. ges. Physiol. **55**:1, 1894.
21. Benedict, F. G., and Carpenter, T. M.: Food Ingestion and Energy Transformations, Carnegie Institution of Washington, D. C., Pub. No. 261, pp. 217, 231.

CASE 1.—Ab. M., an Arabian male, aged 21 years, height 168 cm., weight 40 kg. Acute illness of two months' duration with signs of pneumonic consolation of the entire left lung. Many tubercle bacilli in the sputum. Temperature range, from 100 to 104 F.

CASE 2.—Fred R., aged 41 years, height 167 cm., weight 47 kg. History of chronic cough and loss of weight for three years' duration. Had been hospitalized for eight months. Many tubercle bacilli in the sputum. Marked emaciation, dyspnea and cyanosis. Physical signs of extensive bilateral infiltration with numerous cavities. Confirmation by roentgenogram and necropsy.

CASE 3.—J. O'C., a male, aged 49 years, height 174.3 cm., weight 49.7 kg. History of probable active pulmonary tuberculosis of eleven years' duration. Chronic cough, slow emaciation, and slight hemoptyses. Symptoms became acute and urgent only one month before admission. Physical signs of infiltration of both upper lobes of lungs, more advanced on the right side, with small amount of fluid in the right pleura. Some enlargement of the heart with retraction of the heart to the right. Many tubercle bacilli in the sputum. Temperature range from 97.4 to 102.2 F.

CASE 4.—George R., aged 35 years, height 163.5 cm., weight 57 kg. History of fistula in ano for three years. Pulmonary symptoms of six months duration. Marked constitutional symptoms of only two months' duration—night sweats and loss of weight. Physical and fluoroscopic examination showed marked infiltration of both upper lobes with a large cavity in each. Sputum contained many tubercle bacilli. Temperature range from 98 to 101 F.

CASE 5.—J. V. B., a male, aged 43, height 174 cm., weight 44.4 kg. Symptoms all developed within six months—cough, night sweats, and a loss of weight of 42 pounds. Fluoroscopic examination showed a large cavity in the left upper lobe, below which there was consolidation with multiple excavations. The right middle and upper lobes were densely infiltrated, containing multiple excavations. There was a similar condition in the apex of the right lower lobe. Sputum contained many tubercle bacilli. Temperature range from 98 to 102 F.

The normals used as controls are described briefly as follows:

CASE 6.—John S., laboratory assistant, aged 21 years, height 165 cm., weight 61.5 kg. Subject was fat. Had no symptoms of serious nature during two years in the laboratory. Physical examination and urine examination revealed no abnormalities.

CASE 7.—C. H. L., a female medical student aged 26 years, height 161.1 cm., weight 53.9 kg. Had been in good health during three years of medical course. Physical examination negative. Urine normal.

CASE 8.—W., a male medical student, height 179 cm., weight 73 kg. Large athletic individual in perfect health. Physical examination negative. Urine normal.

CAS' 9.—G. M., physician, female, aged 32 years, height 160 cm., weight 56.05 kg. In perfect health. Physical examination normal. Urine normal.

CASE 10.—Wm. U., a lawyer, aged 42 years, height 179 cm., weight 51.7 kg. Had an abscess in neck in childhood; gonorrhea in 1902; mastoiditis and chronic otitis media from 1914 to 1916; malaria of the quartan type in 1909; in perfect health during experiment. He had undertaken a fasting experiment, which he had done several times before. Between Nov. 28, 1920, and the date of the respiration experiment of Jan. 19, 1921, he had fasted forty-two days in three periods of 10, 16 and 16 days respectively. The experiment given in Table 1 is the breaking of the last sixteen day fast. The meal taken was one of pot cheese which had been washed thoroughly until it was practically free from

carbohydrates. The physical examination was normal, except for emaciation due to fasting. He was 71 pounds under the weight at the start of fasting. November 28. Urine normal.

CONCLUSIONS

1. The total pulmonary ventilation of five cases of advanced pulmonary tuberculosis was approximately twice that of five normal controls. The percentage of carbon dioxid produced and of oxygen absorbed, in terms of expired air, was much reduced as compared with normals.

2. The alveolar ventilation in the tuberculous patients was greater than that of the normal subjects, as was the ratio of alveolar ventilation to the volume of carbon dioxid expired.

3. The ingestion of protein food increased both heat production and total pulmonary ventilation in a corresponding degree in both tuberculous patients and controls. After ingestion of 70 gm. protein (from 40 to 45 gm. per square meter of body surface) heat production was increased from 22 to 29 per cent. and ventilation from 20 to 25 per cent. in tuberculous subjects.

4. In the form of fat the greatest number of calories may be ingested with the least effect on the pulmonary ventilation. Carbohydrates increase the ventilation out of all proportion to their effects upon the general oxidative processes and heat production. This is believed to be due to the relatively greater quantities of carbon dioxid eliminated during carbohydrate oxidation, in other words, to the higher respiratory quotient.

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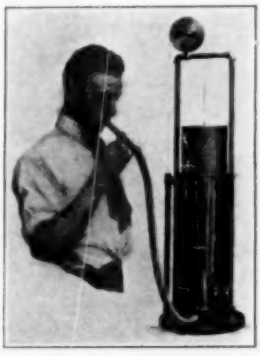

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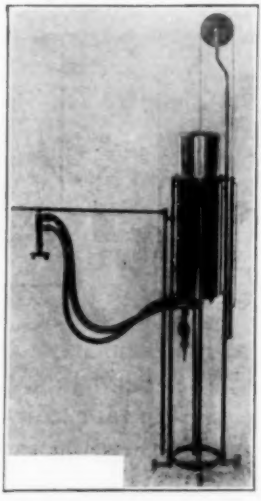

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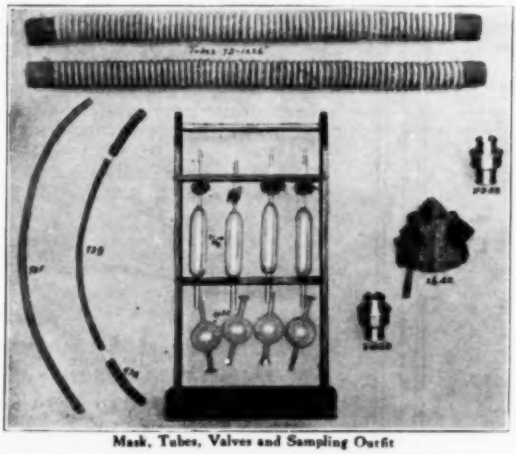

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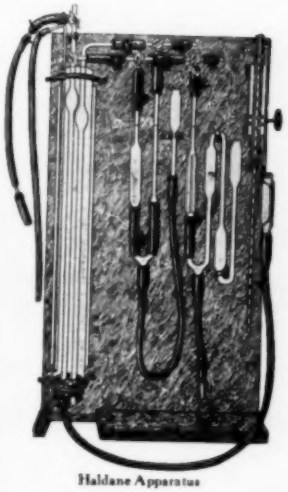

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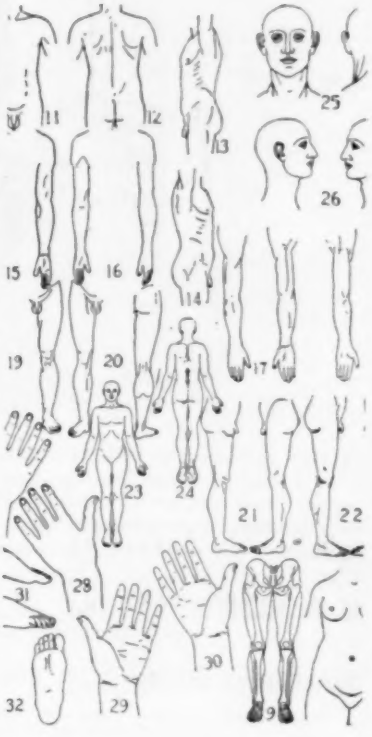

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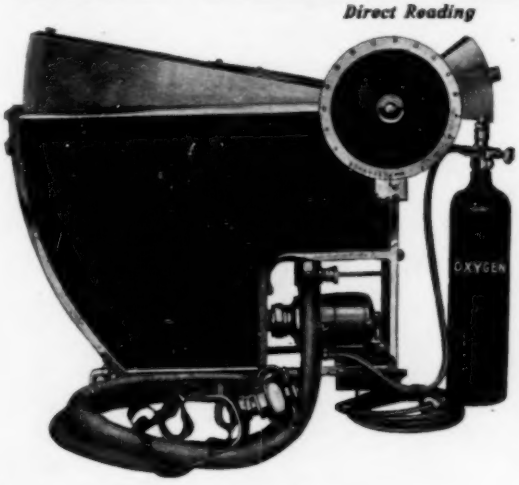

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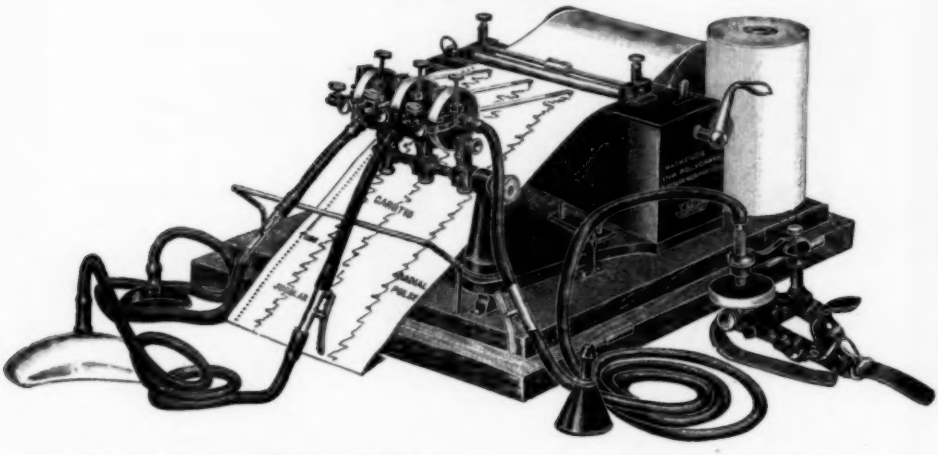

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